# PRESCRIPTION PATTERN OF ANTIBIOTICS IN THE MANAGEMENT OF DIABETIC FOOT ULCER IN OUT PATIENT DEPARTMENT

**Dissertation**

**Submitted to**

**The Tamil Nadu Dr. M.G. R. Medical University, Chennai.**

**In partial fulfillment for the award of the degree of**

**Master of Pharmacy**

**In**

**PHARMACY PRACTICE**

**By**

**MENGE DENIS MINGATE**

**DEPARTMENT OF PHARMACY PRACTICE**

**ULTRA COLLEGE OF PHARMACY**

**4/235, COLLEGE ROAD, THASILDAR NAGAR,**

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**OCTOBER 2013**

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## DECLARATION

I hereby declare that this thesis work entitled **"PRESCRIPTION PATTERN OF ANTIBIOTICS IN THE MANAGEMENT OF DIABETIC FOOT ULCER IN OUTPATIENT DEPARTMENT"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmacy Practice,Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mr. S.K. SATHISH, M.Pharm.,** Asst.Professor, Department of Pharmacy Practice, Ultra College of Pharmacy, Madurai, during the academic year Dec 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not formed the basis for the award of any degree, diploma, associateship, fellowship of any other university or institution.

PLACE: MADURAI (**Reg. No: 26103487**)

DATE:

**ULTRA COLLEGE OF PHARMACY**
**4/235, COLLEGE ROAD,**
**THASILDAR NAGAR,**
**MADURAI.**

# CERTIFICATE

This is to certify that, this thesis work entitled "**PRESCRIPTION PATTERN OF ANTIBIOTICS IN THE MANAGEMENT OF DIABETIC FOOT ULCER IN OUTPATIENT DEPARTMENT"** submitted in partial fulfilment of the requirements for the award of degree of Master of Pharmacy in Pharmacy Practice of The Tamil Nadu Dr. M.G.R Medical University, Chennai is a bonafide work carried out by **Reg.No:26103487**and was guided and supervised by me during the academic year Dec 2012-Oct 2013.

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**Dr.C.VIJAYA,**
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**EXAMINERS:**

1.

2.

PLACE: MADURAI

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## ACKNOWLEDGEMENT

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## ABBREVIATIONS

| | | |
|---|---|---|
| DM | - | Diabetes Mellitus |
| MODY | - | Maturity onset diabetes of the young |
| ICA | - | Islet Cell antibodies |
| TIDM | - | Type 1 Diabetes Mellitus |
| T2DM | - | Type 2 Diabetes Mellitus |
| DFU | - | Diabetic Foot Ulcer |

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# INTRODUCTION

**WHO** defines 'Diabetes' as a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.[1]

## EPIDERMIOLOGY

In India, there are thirty-five million diabetic patients and is forecast to have a staggering seventy-three million patients on account of increased life expectancy, sedentary lifestyle and dietary patterns by 2025.

Diabetes continues to be the single most common underlying factor related to lower-extremity amputation in the U.S. and Europe. The incidence of lower-extremity amputation increases with age. Amputations are significantly more common in men than in women, and the incidence and proportion of lower-extremity amputations is significantly higher in minorities.

## ETIOLOGY[2]

The etiology of type 1 diabetes mellitus has been the subject of considerable research. Genetic factors are important but do not explain the full development of type 1 diabetes. There is a strong immunological component to type 1 diabetes and a clear association with many organic specific autoimmune diseases. Circulating islet cell antibodies (ICAs) are present in more than 70% of type 1 diabetics at the time of diagnosis. Family studies have shown that appearance of ICAs often precedes the onset of clinical diabetes by as much as 3 years. Type 1 diabetes has been widely believed to be a slow process of progressive immunological damage.

### Type 1 diabetes

Type 1 diabetes mellitus is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency. Over 95 percent of persons with type 1 diabetes mellitus develop the disease before the age of 25, with

an equal incidence in both sexes. A family history of type 1 diabetes mellitus, gluten enteropathy (celiac disease) or other endocrine disease is often found.

It can be classified into two types:

i. Immune mediated
ii. Idiopathic

**Type 2 diabetes**

Type 2 diabetes mellitus is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in blacks, Hispanics and Native Americans. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Defective beta cells become exhausted, further fuelling the cycle of glucose intolerance and hyperglycemia. The etiology of type 2 diabetes mellitus is multifactorial and probably genetically based, but it also has strong behavioural components.

- **Gestational diabetes**
- **Other specific types**
    - **Maturity onset diabetes of the young (MODY)**
        - Currently 6 monogenetic defects of beta cell function defined with defects in islet cell glucokinase or in various transcriptions factors such as HNF-1alpha, HNF-4alpha, IPF-1. The end result is impaired insulin release and hyperglycemia.
        - Autosomal dominant pattern. Onset of hyperglycemia generally before age 25.
    - **Genetic defects in insulin action**
        - Mutant insulin gene, insulin exhibits impaired receptor binding (rare).

- Mutation of insulin receptor. Often associated with acanthosisnigricans (thickening and discoloration of skin) and some forms of polycystic ovarian syndrome (uncommon).

- **Diseases of the exocrine pancreas**

  - Need extensive damage to pancreas for diabetes to occur
  - Includes trauma, infection, chronic necrotizing pancreatitis and pancreatic carcinoma, cystic fibrosis and hemochromatosis.
  - May be another mechanism besides simple beta cell reduction since cancers which involve a small part of the pancreas may lead to diabetes (paracrine inhibition of insulin release).

- **Endocrinopathies**

  - Includes acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma.
  - Caused by excess secretion of hormones which antagonize insulin including growth hormone, cortisol, glucagon and epinephrine.

- **Drug/chemical induced diabetes**

  - Many drugs may impair insulin resistance or insulin secretion leading to diabetes in predisposed individuals.
  - Major drugs include synthetic glucocorticoids, cyclosporine A, nicotinic acid, interferon, pentamidine, occasionally thiazide diuretics.

- **Infections**

  - Congenital rubella is the most common virus implicated in the development of diabetes.

- Coxsackievirus B, adenovirus, mumps and cytomegalovirus have all been implicated in inducing certain cases of the disease.

**PATHOGENESIS OF DIABETES[3]**

T1DM is an autoimmune condition in which the insulin-producing β-cells of the pancreas are destroyed and hence the body loses its ability to produce insulin. Previously known as juvenile diabetes, T1DM is usually diagnosed in children and young adults, affecting only approximately 5% of the overall diabetes population. T1DM is believed to be an immunological disease where little is known about its risk factors. Nevertheless, epigenetic factors are possible contributors to the development of the disorder. Researchers have also suggested that viral-mediated autoimmunity may also trigger self-destruction or infection of the pancreatic islet cells. Without the help of insulin therapy, T1DM is generally fatal. As such, T1DM patients are entirely dependent on daily multiple insulin administration to sustain life. Alternatively, individuals with T1DM may opt for procedures such as pancreatic or pancreatic islet-cell transplantation to replace the non-functional insulin-producing cells.

T2DM, is the most common form, which accounts for 90–95% of all diabetic cases. Besides family history and genetic factors, risk factors for T2DM include obesity, high blood pressure and high cholesterol levels. T2DM occurs when the sensitivity of the peripheral tissues is compromised such that they can no longer respond appropriately to insulin, a condition also known as insulin resistance. Defects in insulin sensitivity and insulin secretion cause glucose to accumulate in the blood. Over time, the response of the peripheral tissues to insulin becomes progressively blunted and the balance between insulin output and demand is disrupted, thus aggravating the condition. On the other hand, it has also been suggested that β-cell dysfunction observed in T1DM patients can also occur in T2DM.

**CLINICAL MANIFESTATION**

Symptoms are similar in type 1 and type 2, but may vary in their intensity. Common symptoms include polyuria and polydipsia which is a consequence of osmotic diuresis secondary to sustained hyperglycemia. Another consequence of

hyperosmolar state is blurred vision, usually due to a change in refraction. Fatigue and weight loss may occur due to the breakdown of body protein and fat as an alternative source to glucose.

**A. Type 1 diabetes**

If the diagnosis is not made when the common features of hyperglycemia are present, diabetic ketoacidosis may develop. Ketoacidosis may exacerbate the dehydration and hyperosmolarity by producing anorexia, nausea and vomiting. As the plasma osmolarity rises, impaired consciousness ensues. With progression of the acidosis, deep breathing with a ventilatory rate (Kussmal respiration) occurs as the body attempts to correct acidosis. The patient's breath may have a fruity odour of acetone.

**B. Type 2 diabetes**

Along with common symptoms of polyuria and polydipsia, weight loss, chronic skin infection is common, as sustained hyperglycemia can result in severe impairment of phagocyte function. Generalized pruritis and symptoms of vaginitis are frequently the initial complication in women with type 2 diabetes. Occasionally patients will present themselves when the complication of sustained hyperglycemia has already developed. Retinopathy may be detected on routine ophthalmological or the combination of neuropathy, peripheral vascular disease and infection may manifest as foot ulceration or gangrene.[4]

**DIAGNOSIS**

When symptoms suggest diabetes, the diagnosis may be confirmed by a random serum glucose concentration of greater than 11 mmol/l 2hours after 75g anhydrous glucose is given. Hyperglycemia during pregnancy is abnormal and requires careful assessment.

In those with stress hyperglycemia, the blood glucose level should be re-measured on recovery from acute illness, when it should have returned to normal.

When the diagnosis is confirmed, other investigations should include test for urea, creatinine, electrolysis, liver function tests, cholesterol and triglycerides and urine testing for protein microalbuminuria.

## COMPLICATIONS

Treatment aims initially to relieve the immediate signs and symptoms of diabetes like polyuria, polydipsia, weight loss and ketoacidosis. In the longer term, the main aim of treatment is to prevent the development, or slow the progression of the long-term complication of the disease. Treatment should also aim to minimize the occurrence of hypoglycemia. Persistent hyperglycemia and hypertension are the two major controllable factors that influence the development of diabetic complications. These can be divided in to those caused by microvascular disease and those secondary to macrovascular disease.

Complications due to diabetes are:

1. Eye disease
2. Disease of the urinary tract
3. Nerve damage
4. Diabetic foot
5. Cardiovascular disease.

There is a whole spectrum of rare complications that can occur in diabetics. These include musculoskeletal problems e.g. Dupuytren's contracture and Charcot's arthropathy and dermatological condition e.g. Acanthosis nigricans and Necrobiosis lipoidica. In addition to all these chronic complications, the patient with diabetes may also be at risk of experiencing the acute complications of hypoglycemia, diabetic ketoacidosis and non-ketotic hyperglycemic coma.[5]

## DIABETIC FOOT ULCERATION

Diabetic foot complications are the most common cause of nontraumatic lower extremity amputations in the industrialized world. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in persons who do not have diabetes mellitus.

The vast majority of diabetic foot complications resulting in amputation begin with the formation of skin ulcers. Early detection and appropriate treatment of these ulcers may prevent up to 85 percent of amputations.

By the year 2025, diabetics worldwide will be 250 million as compared to 120 million in 1996. With the onset of diabetic sensory neuropathy, the feet of many of

these people will be at risk of foot ulceration. It has been found that foot ulcer precedes 85% of non- traumatic amputations in diabetics.

Foot infection is the most common reason for hospitalization among diabetic patients accounting for up to 25% of admissions. Regrettably, less than 14% of patients admitted for diabetic foot complications receive adequate lower extremity evaluation, and when foot ulcers do develop, one in five of these patients eventually have to undergo amputation. It has been estimated that with appropriate knowledge of risk factors and treatment by a multidisciplinary team, up to 85% of foot and leg amputations in diabetic patients could be prevented.[6]

Neuropathy and ischemia are the principal disorders underlying foot problems. Whenever a patient presents with an active lesion, it is essential to decide at an early stage where the foot problem is.

Photographs showing an ulcer on the toes.

**Precipitating causes of foot ulceration and infection.**

Patients who have the following characteristics are at high risk of developing foot complications:

- Peripheral neuropathy
- Peripheral arterial disease
- Previous foot ulceration or amputation
- Structural foot deformity
- Plantar callus
- Older age (>70 years)
- Māori or Pacific ethnicity
- Longer duration of diabetes
- Smoking
- Other diabetic complications e.g. retinopathy
- Renal impairment
- Continual use of inappropriate footwear
- Living in a lower socio-economic area.

A combination of ulceration and sepsis in an ischemic foot carries a higher risk of gangrene, and early arterial assessment and management are the keys to avoiding major amputation.

Men of low socio-economic class are the most prone to diabetic disorders and Asian patients least likely to get them. Many causes are avoidable. Patients confined to bed must have their heels elevated to avoid heel blisters and sepsis. Such wound need weeks or months to heal.[7]

Diabetic foot problems, which account for more hospital admissions than any of the other long-term complications of diabetes, are associated with increasing morbidity and mortality in diabetic patients. They tend to occur in about 20% of the diabetic population and the costs of services, direct and indirect that is associated with the management of the diabetic foot. Diabetic foot problems are responsible for more than two-thirds of all non-traumatic lower limb amputations.[8]

Foot ulcerations, infections and Charcot's neuropathic osteo-arthropathy are three serious foot complications of diabetes mellitus that can too frequently lead to gangrene and lower limb amputation. Consequently, foot disorders are one of the leading causes of hospitalization for persons with diabetes and can account for expenditures in billions of dollars annually in the U.S. alone. Although not all foot complication of diabetes mellitus that can be prevented, dramatic reductions in their

frequency have been obtained through the implementation of a multidisciplinary team approach to patient management.

Administration of prompt and appropriate care for diabetic foot ulcerations is necessary to reduce complications, which may lead to limb loss. An understanding of standard, appropriate and advanced care may assist the physician in making the most optimal decision when treating diabetic foot ulcers. An overview of the diabetic foot, its associative problems, considerations when reviewing the diabetic patient individually to determine their specific their specific antibiotic sensitivity and choose an appropriate drug, which the organisms are susceptible to.

## EPIDERMIOLOGY OF ULCERATION AND AMPUTATION

Of the three crore diabetic population in our country, 15% suffer from diabetic foot problems. Approximately 15% of persons with diabetes will have an ulcer in their lifetime and 0.5% to 29% will have neuropathic joint changes.

## ETIOLOGY OF FOOT ULCERATION

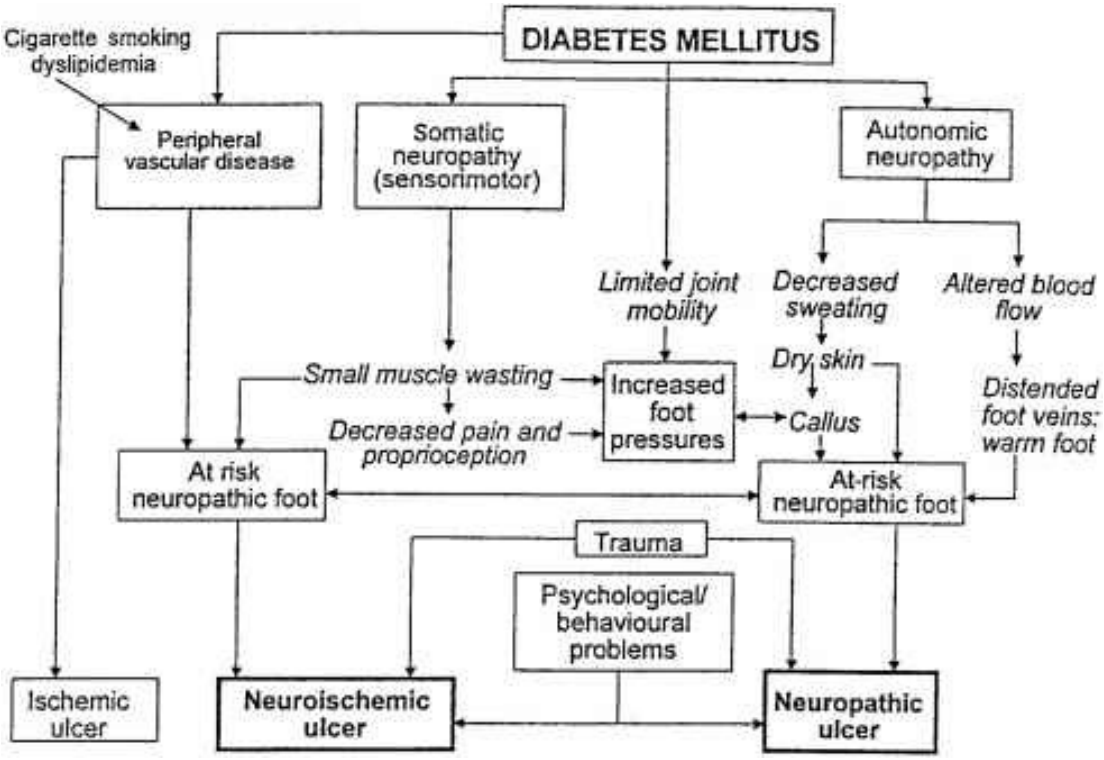
In India, diabetic foot disease is exacerbated by socio-cultural factors such as the prevalence of walking barefoot, lack of knowledge regarding diabetic foot complications, and the socio-economic status of patients.

The etiology of diabetic foot ulcers usually has many components. A recent multicenter study attributed 63% of diabetic foot ulcers to the critical triad of peripheral sensory neuropathy, trauma and deformity. Other factors in ulceration are ischemia, callus formation and edema. Although infection is rarely implicated in the etiology of diabetic foot ulcers, the ulcers are susceptible to infection once the wound is present. Many risk factors for foot ulcers are also predisposing factors for amputation, because ulcers are primary causes leading to amputation.

## PATHOPHYSIOLOGY OF DIABETIC FOOT INFECTION

A diabetic foot infection is simply defined as any inframalleolar infection in a person with diabetes mellitus. These include paronychia, cellulites, myositis, abscesses, necrotizing fasciitis, septic arthritis, tendonitis and osteomyelitis. The most common and classical lesion, however, is the infected diabetic “mal perforans” foot ulcer. Neuropathy plays the central role, with disturbances of sensory, motor and

autonomic functions leading to ulceration due to trauma or excessive pressure on a deformed foot that lacks protective sensation. Once the protective layer of the skin is breached, underlying tissues are exposed to bacterial colonization. This wound may progress to become an actively infected wound, and by contiguous extension, the infection can involve deeper tissues. This sequence of events can be rapid, occurring over hours or even days, especially in an ischemic limb. Various poorly characterized immunologic disturbances, especially those that involve polymorph nuclear leucocytes, may affect some diabetic patients, and these are likely to increase the risk and severity of foot infections.




## ULCER EVALUATION

A thorough evaluation of any ulcer is critical and should direct the management. An adequate description of ulcer characteristics, such as size, depth, appearance, and location, also provides mapping of progress during treatment. The evaluation should determine the etiology of the ulcer and ascertain whether the lesion is neuropathic, ischemic, or neuro-ischemic. Failure to perceive the pressure of 10-g

monofilament is proven indicator of peripheral sensory neuropathy and loss of protective sensation.

**Ulcer evaluation using a 10g-monofilament.**

Other common modalities that can detect insensibility are a standard tuning fork; i.e., 128 cycles per second and neurological reflex hammer.

After describing the dimensions and appearance of the ulcer, the physician examines the ulcer with a blunt sterile probe. Gentle probing can detect sinus tract formation, undermining of ulcer margins, and dissection of the ulcer into the tendon sheaths, bone, or joints. A positive probe-to-bone finding has a high predictive value for osteomyelitis. Failure to diagnose underlying osteomyelitis often results in failure of wound healing. The existence of odor and exudates, and the presence and extent of cellulites must be noted.

Aerobic and anaerobic cultures should be taken when signs of infection, such as purulent drainage material from the ulcer base.

The foot and ulcer examination should include the following:

(1) Assessment of dermatologic changes in the surrounding skin, including callus, musculoskeletal deformity and muscle wasting.

(2) Documentation of ulcer characteristics, including location, shape, and size of the wound (measurement of length, width, and depth).

(3) Determination of the condition of the wound edges, wound bed, wound base, periwound skin, and exudates.

(4) Determination of the presence of necrosis and wound-associated pain.

Evaluation for complications, such as cellulitis, gangrene, osteomyelitis, or Charcot deformity (neuropathic osteoarthropathy) should also be performed.

**INVESTIGATIONS**

Radiographs should be obtained in most patients with deep or longstanding ulcers to rule out osteomyelitis; however radiographs are not a very sensitive indicator of acute bone infection. When clinical suspicion indicates osteomyelitis but radiographs are negative, additional bone or leukocyte scanning is helpful in ascertaining bone involvement. However, in the neuropathic patient, bone scans are often falsely positive because of hyperemia or Charcot's arthropathy. Leukocyte scanning or magnetic resonance imaging offers better specificity in this situation. Ultimately, bone biopsy is necessary to firmly establish the diagnosis of esteomyelitis.

**DIABETIC FOOT ULCER CLASSIFICATION[9]**

DFU is classified as

**(A) University of Texas at San Antonio Diabetic Wound Care Classification System**

| Grade | Description of Wound |
|---|---|

| | |
|---|---|
| A0 | Pre- or post-ulcerative lesion completely epithelialized |
| A1 | Superficial wound, not involving tendon, capsule, or bone |
| A2 | Wound penetrating to tendon or capsule |
| A3 | Wound penetrating to bone or joint |
| | Pre- or post-ulcerative lesion completely epithelialized with infection |
| | Superficial wound, not involving tendon, capsule, or bone with infection |
| B2 | Wound penetrating to tendon or capsule with infection |
| B3 | Wound penetrating to bone or joint with infection |
| | Pre- or post-ulcerative lesion, completely epithelialized with ischemia |
| | Superficial wound, not involving tendon, capsule, or bone with ischemia |
| C2 | Wound penetrating to tendon or capsule with ischemia |
| C3 | Wound penetrating to bone or joint with ischemia |
| | Pre- or post-ulcerative lesion completely epithelialized with infection and ischemia |
| | Superficial wound, not involving tendon, capsule, or bone with infection and ischemia |
| | Wound penetrating to tendon or capsule with infection and ischemia |
| | Wound penetrating to bone or joint with infection and ischemia |

**(B) Wagner Classification System for Diabetic Foot Ulcer**

| Grade | Lesion |
|---|---|

| | |
|---|---|
| 0 | No open lesions: may have deformity or cellulitis |
| 1 | Superficial ulcer |
| 2 | Deep ulcer to tendon or joint capsule |
| 3 | Deep ulcer with abscess, osteomyelitis, or joint sepsis |
| 4 | Local gangrene – forefoot or heel |
| 5 | Gangrene of entire foot |

**(C) Liverpool classification system for DFU**

**Primary**

- Neuropathic
- Ischemic
- Combination of both

**Secondary**

- Uncomplicated
- Complicated i.e. presence of Cellulites, Abscess or Osteomyelitis

**TREATMENT**

Preparing the wound for healing may include debridement, control of infection and inflammation, moisture control, and excision of wound edges and periwound callus, when appropriate.

**Debridement**

This involves the removal of nonviable tissue, matrix metalloproteinases (MMPs) and biofilm, and the excision of wound edges and periwound callus to stimulate the production of growth factors. Debridement may be surgical, enzymatic (collagenase), autolytic (ie, occlusive), mechanical (wet-to-dry dressing, lavage), or biologic (larval). Wound debridement is traditionally performed initially and then may be performed at weekly intervals (maintenance debridement). If the ulcer bed is clean, shows beefy red granulation tissue, and is free of infection, maintenance debridement may not be required.

**Infection Control**

Patients with diabetes are typically immunocompromised and often fail to mount a physiologic response to infection, clinicians should look for secondary signs of infection including exudates, delayed healing, friable granulation tissue, discolored granulation tissue, foul odor, pocketing at the wound base, and wound breakdown. Infections in DFUs are usually polymicrobial, predominantly comprising aerobic, Gram-Positive, Cocci. *Staphylococcus aureus* is the most common pathogen found in chronic, nonhealing DFUs. Optimal treatment decisions can be made only after determining the causative organism(s). Tissue cultures have remained the gold standard of bacterial identification for many years.

**Off-Loading**

The use of effective off-loading modalities is a very important part of DFU treatment and their value should not be underestimated. High-level evidence is lacking that wheelchairs, bed rest, crutches, custom shoes, therapeutic shoes, pads, or custom-made insoles can heal wounds. In some cases devices can interfere with healing; a completely circular felt donut pad can occlude the entire superficial blood supply to the wound via the “edge effect.” most patients with DFUs have significant neuropathy and they strike the ground more rapidly than those without neuropathy. For a device to be effective in decreasing the rate and absorbing the force, it must extend above the ankle.

The literature supports the following devices as having reproducible ability to heal wounds: cast walkers, Charcot Restraint Orthotic Walkers (CROW)/total contact brace, patellar tendon-bearing (PTB) braces, ankle-foot ortheses (AFOs) in shoes, and regular or instant total contact casting (TCC). These methods work because they decelerate the foot onto the ground, and decrease weight bearing if they are used for walking.

Appropriate offloading is a key component in the management of diabetic foot disease. The use of TCCs has been reported to result in excellent ulcer healing rates and associated with faster healing compared to other removable devices in a randomised controlled trial. The TCC is considered to be the gold standard offloading device for plantar neuropathic ulcers, yet it is still not widely used in clinical practice.

It works by transmitting load from the forefoot to the heel and directly to the leg via the cast walls. Its main disadvantage is that its application is time-consuming and often associated with a learning curve.

Removable cast walkers are cast-like devices that are removable to allow inspection of the wound and application of topical therapies. Further, removable cast walkers can be easily converted into instant total contact casts by wrapping the removable cast walker with cohesive bandage or plaster of Paris.[10]

Diabetic foot ulcers cause considerable morbidity and mortality. It is estimated that approximately 6% of all diabetic patients have had a history of foot ulceration.

1. Ulcer infections are the leading cause of lower extremity limb loss.
2. Ulcer healing is thought to be affected both by the number of bacterial groups and by bacterial density.
3. Adequate infection management is intended to aid ulcer healing and reduce the risk of amputation. This must be done in conjunction with debridement, wound dressing; pressure relief, adequate glycaemic control and optimization of vascular supply.
4. Widespread use of antibiotics may result in several problems including the spread of antibiotic resistance and side effects which, although generally minor, can occasionally be severe and even life threating.

Regular examination of both the feet,looking for bony prominence differences in temperature, foot pulses, dry skin, callus, bunions and overgrown toe nails will help in early detection of pre-ulceration. Classification of foot ulcers is necessary for the prognosis and management.

**Podiatrist checking for ankle pulses.**

A mainstay of ulcer therapy is debridement of all necrotic and fibrous tissue to allow full visualization of the extent of the ulcer and detect the underlying abscesses or sinuses. Topical enzymes have not been proved effective for this purpose and should only be considered as adjuncts to sharp debridement.

Soaking ulcers is controversial and should be avoided because the neuropathy patient can easily be scaled by hot water. Although numerous topical medications and gels are promoted for ulcer care, relatively few have proved to be more efficacious than saline wet dry dressings.

Topical antiseptics, such as povidone-iodine, are usually considered to be toxic healing wounds. Generally, a warm, moist environment that is protected from external contamination is most conducive to wound healing. This can be provided by a number of commercially available special dressings, including semi permeable films, foams, hydrocolloids, and calcium alginate swabs.

The treatment for diabetic foot depends upon the grade of diabetic foot, level of intervention, vascular intervention, infrastructure of the hospital and expertise. While an intermediate surgery costs around rupees eight thousand to rupees ten thousand, a major surgeries cost as high as rupees twenty thousand to rupees twenty

five thousand. The cost can soar higher in case vascular block, where the angiography of the legs and revascularization with angioplasty or bypass is required. Repeated surgeries coupled with long hospital stay and use of antibiotics is a major contributor to expense of the treatment of diabetic foot.[11,12]

When hospitalized patient is ready for discharge or outpatient returns for follow up, clinician should accomplish 4 tasks.

**1. Select the definite antibiotic regimen**

Review the culture and drug susceptibility results and enquire about any adverse effects relate to the current antibiotic therapy. Choose the definitive antibiotic therapy regimen (including the treatment duration) on the basis of results cultures, imaging, or other investigations and clinical response. It is not always necessary to cover all microorganisms isolated from cultures. More virulent species should always be covered.

**2. Re-evaluate the wound**

Inspect the site to ensure that infection is responding and the wound is healing. No evidence supports giving antibiotics for the entire time that the wound remains open. Antibiotics should be used for a period defined by the biology of the infection and by the clinical syndrome.

**3. Review the offloading and wound care regimens**

Determine the effectiveness of, and the patient's compliance with, the prescribed regimens. Suggest alternatives when necessary.

**4. Evaluate glycemic control**

Ensure that blood glucose levels and other aspect of patient's metabolic status are adequately controlled.[13]

**New therapeutic approaches to foot ulcers**

Frequent examination of the diabetic foot, identifying risk factors and the regular follow-up in a specialist foot clinic are important in the management of the "diabetic foot". Early diagnosis, wound care and pressure relief will help reduce amputations. It should be remembered that the new wound-healing therapies (e.g.

growth factors, artificial skin) are no substitute for basic wound care, i.e. wound debridement, offloading, treating infections and revascularization. The importance of a multidisciplinary team approach to foot care in patients with diabetic foot problems cannot be over-emphasized.

Treatment that may potentially prevent the development of foot ulcerations, such as footwear and silicone injection, will be considered first. This will be followed by specific therapies for the management of patients with active foot ulcers.

- Topical hyperbaric oxygen therapy
- Therapeutic footwear
- Skin graft
- Retrograde venous perfusion
- Platelet-derived growth factors
- Low intensity laser therapy
- Larval therapy
- Injected liquid silicone
- Follow-up education: the multidisciplinary approach to foot care.
- Antibiotic-impregnated calcium sulphate pellets

The real approach in the management of diabetic foot ulcers is not just healing them, but keeping them healed. Despite all efforts geared towards the treatment of diabetic foot, these problems still recur. It was confirmed the value of multidisciplinary approach to education and self-care diabetic patients in reducing the incidence of foot lesions in general practice. A recent prospective study has also demonstrated the effectiveness of multidisciplinary approach to diabetic foot care. Recurrence rates were considerably reduced by regular follow-up by a team physicians, nurses and podiatrists, with re-education every three months and provisions of special footwear as required.

## ANTIBIOTICS AND DEVELOPMENT OF RESISTANCE

Emergence of strains of bacteria resistant to currently available anti-microbial compounds contribute to increased morbidity, mortality, and healthcare costs. Antibiotic resistance is one of a number of reasons why antibiotic therapy can fail. Through appropriate antibiotic administration and effective implementation of infection control practices, physicians can help stem the tide of increasing bacteria resistance. Alternative novel approaches should be developed to prevent and treat bacterial infections. Ancillary therapies merit increased attention, since these adjunctive measures can exert a critical role in successful management of bacterial infections.

### Mechanisms of anti-microbial resistance

- Permeability changes in the bacterial membrane or cell wall, thereby restricting drug access to target sites.
- Efflux pumps that actively extrude anti-microbial agent from the cell.
- A mutation at the target site.
- Enzymatic degradation of the drug
- Development of alternative metabolic pathways by the bacterium, thereby negating the inhibitory impact of anti-microbial.

### Reason for antibiotic resistance strategies to prevent resistance[13]

For more than 50 years, physicians worldwide have relied on antibiotics for rapid and effective management of many of the most common infections. Anti-microbial agents have changed the way both physicians and the public perceive bacterial infections and their treatment.

Patients may add to problem of antibiotic resistance when they don't take full course of a prescribed drug. Many people stop taking anti-microbial agents when their symptoms improve, even though the infectious organisms may not have been eradicated completely. Then they will store the remaining mediation for future use when they (or a family member) develop another illness, even though the new ailment may not be the one for which antibiotics are appropriate-particularly in a shortened course that is not therapeutically effective. Incomplete treatment can lead to treatment failure or recurrence of symptoms, while also encouraging the growth of resistant strains.

At the summit on Anti-microbial Resistance, participants discussed in depth many of the worrisome trends in resistance, including the growing number of drugs to which some organisms are resistant. Over 90% of strains of *S. aureus* demonstrate resistance to penicillin and related anti-microbial agents. It is not uncommon for certain microorganisms to become multi drug resistant, sometimes insensitive to more than 10 antibiotics. For example, certain strains of three species: *Enterococcus faecum, Mycobacterium tuberculosis and Pseudomonas aeruginosa*- are resistant to nearly every available antibiotic, which is particularly ominous because they are associated with potentially life threatening diseases.

At the summit on Anti-microbial Resistance, primary care physicians and infectious diseases specialists drafted a blue for action, incorporating a series of recommendations for community physician to help turn the tide on antibiotic resistance.

The anti-microbial resistance problem in hospitals continues to worsen. In particular, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) is significant because of morbidity and mortality among critically ill patients. Treating infections caused by these pathogens presents therapeutic dilemmas. The association between broad-spectrum β-lactam over utilization and selection for ESBL-KP has been appreciated for some time; several institutions have reported a decrease in the prevalence of ESBL-KP with shift in antibiotic utilization from third-generation cephalosporins to other broad-spectrum drugs.

**Strategies to limit anti-microbial resistance are**

- Do not indulge patient demand for unneeded antibiotics.
- Educate on appropriate antibiotic use
- Identify the pathogen
- Choose short-course antibiotics, narrow-spectrum antibiotics
- Complete the full course of therapy
- Use antibiotics for prophylaxis prudently
- Follow proper hygiene procedures
- Encourage patients to get vaccinated
- Improve resistance surveillance systems
- Use antibiotics judiciously in non-human settings
- Advocate new drugs development

**Prescribing practice**

Each time an antibiotic is used; it may contribute a little to the environment pool of resistance bacteria. Not surprisingly, as the number of prescriptions has risen, so as has the incidence of resistance. As a result, the empiric management of many infections has become more difficult in some geographic regions where resistance to organisms has become more prevalent. Some community and hospital-acquired bacteria strains have developed resistance to so many antibiotics that choosing an effective agent for certain serious infections are becoming more challenging.

Additional factors have been cited as contributors to inappropriate antibiotic use and ant-microbial resistance. For instance, physicians may worry about losing patients if they decline to prescribe. They might prescribe antibiotics inappropriately due to pressure from patients or parents who want to return to work to return to work sooner. Some doctors could have inadequate knowledge about who should or shouldn't receive these drugs. Physicians in managed care settings might feel pressure to cut costs by providing drug therapy rather than ordering diagnostic tests. Some physicians also over prescribe because of concerns that may misdiagnose a bacterial infection for which an antibiotic is appropriate.

Appropriate monotherapy for cellulites includes cefazolin or clindamycin. Although gram-negative organisms are the unusual causes of cellulites, even in diabetes, if they are suspected, a fluoroquinolone eg. levofloxacin, may be used in conjunction with clindamycin.

In patients with diabetes, deep skin and severe soft tissue infections are usually due to mixed aerobic and anaerobic organisms. These infections may be treated with monotherapy involving meropenem or piperacillin and tazobactum. Alternatively, clindamycin plus levofloxacin or metronidazole may be used.

In acute osteomyelitis, which is usually is due to *S. aureus*, may be treated with cefazolin, clindamycin, and antistaphylococcal penicillin eg, nafcillin.

In chronic osteomyelitis, coverage must be directed against *S.aureus*, group A and group B *Streptococci*, aerobic gram-negative bacilli, excluding *P.aeruginosa*, and *B.fragilis*. Monotherapy for chronic osteomyelitis may include ampicillin and sulbactam, piperacillin and tazobactam, or meropenem. In chronic osteomyelitis,

antimicrobial therapy without adequate debridement does not eliminate the infection. Combination therapy for diabetic foot infections involves levofloxacin plus clindamycin.

# LITERATURE REVIEW

In a study conducted by **S.M Ali et al. (2001)** on 100 patients they found that there were 65% males and 35% females. Ninety nine patients were type 11 diabetics. Awareness about risk factors causing foot problems was lacking among all patients. Fifty percent patients were on oral hypoglycaemic agents, 48% were insulin treated, while 2% were on diet and exercise alone. Glycaemic control was poor in 70%, fair in 16% and was good in 14%, 31% were overweight and 5% patients were underweight. Duration of diabetes was greater than ten years in 58%, toes were affected in 44% sole/metatarsal in 18%; rest included malleoli, heel etc. Eleven patients had ulcers on both feet. Neuropathic ulcer were 42%, neuro-ischaemic 58%, Sixty nine percent patients were in the age group between 40-60 years. Cause was unknown 29% blisters and boil 14%, trauma/cutting 17%, burns 8%, dry skin/callus 10%. Fundal changes were present in 37%; proteinuria in 37%, ischaemic heart disease in 20%, hypertension 18%. In 60% more than one antibiotic was used. Foot ulcers of fifty nine patients healed on conservative management, six patients had below knee amputation, fifteen had toe amputation; nine were still on treatment, eleven lost contact.[14]

**William J Jeffcoate et al. (2003)** conducted a study in a cohort of 558 people, and found that only 345 (62%) healed after primary treatment; 123 (22%) healed after surgery and 90 (16%) died unhealed. In deep infections, the rate of healing without surgery can drop to 40%,with a median healing time of 24 weeks; with surgery this rate increases to 52 (minor amputation) and 38 weeks (major amputation). Of 389 ulcers (in 179 people, newly referred) only 33% healed without surgery within 3 months. Of those followed up for 6 months, 48% healed without surgery, while 40% were unhealed; six patients lost a lower limb; and ten died. Rates and speed of healing are best in ulcers that are mainly a result of neuropathy. In trials of off-loading techniques, 21–50% of patients healed within 30 days, and 58–90% within 12 weeks.[15]

**Benjamin G Fincke et al. (2010)** conducted a study on 3,792 patients and found that patients had cellulitis/abscess of the foot either alone (16.4%), or with ulcer (32.6%), osteomyelitis (19.0%) or gangrene (32.0%). Antibiotics were prescribed for 98.9%. At least 5 continuous days of treatment with an unchanged regimen of one or more antibiotics was prescribed for 59.3%. The means and (ranges) across facilities of the three most common regimens were: 16.4%, (22.8%); 15.7%, (36.1%); and 10.8%, (50.5%). The range of variation across facilities proved substantially greater than that across the different categories of foot infection. They found similar variation in the spectrum of the antibiotic regimen.[16]

**Jain Manisha et al. (2012)** conducted a study on 125 patients in which 85 were male patients and 40 were female patients. Out of 125 specimens, 108 specimens showed growth of organisms. A total of 157 aerobic organisms were isolated from culture positive specimens. It represented an average of 1.25 organisms per case. Among these organisms, 130 gram negative and 27 gram positive organisms were isolated. *Pseudomonas aeruginosa* (30.57%) was predominant organism followed by *Klebsiella spp*. (22.29%). *Staphylococcus aureus* were 12.74% in which Methicillin resistant *S. aureus* (MRSA) was 55%.They concluded that *Pseudomonas aeruginosa* (30.57%) was the most common isolate. Organisms in mixed infections showed multidrug resistance as compared to single isolated strain. Diabetic foot infections are polymicrobial in nature. As the Wagner's grade increased, the prevalence of isolates also increased.[17]

**J. Vimalin Hena et al. (2010)** conducted a microbial study for aerobic organisms from 100 cases of diabetic foot ulcers to determine the etiological agents and their antibiogram. Polymicrobial infection was observed in all the cases. Of the total 100 diabetic foot patients studied 69 were males and 31 were females, the male: female ratio being 2:1. Their ages ranged from 35 years to 85 years with an average of 58 years. The maximum number of patients having diabetic foot infections belonged to the age group of 56-65 years, the cases was with diabetes mellitus for more than a decade. 48 patients had other complications, such as peripheral vascular disease, neuropathy, nephropathy, retinopathy, cataract, ischaemic heart disease or hypertension along with diabetes mellitus. Peripheral neuropathy had a central role

and was present over 80% of diabetic patients with foot lesions. From the 100 patients studied, aerobic bacteria in the pure form were isolated in all the cases in which 47 were *S. aureus*, 3 were *C. koseri,* 17 were *E. coli*, 10 were *K. pneumoniae*, 27 *P. aeruginosa*, 7 were *P. vulgaris*.Over 63.8% strains of *S.aureus* were sensitive to gatifloxacin. Only 25.5% of strains were sensitive to ciprofloxacin. While *E. coli* was highly sensitive to the antibiotics tested, *Pseudomonas* was highly resistant to them.[18]

According to **Asha Konipparambil Pappu et al. (2011)**on a study conducted among 104 diabetic foot ulcer patients admitted, *Pseudomonas* was isolated in 23% of the samples. *Staphylococcus aureus* (21%), *Klebsiella* (17%), *Proteus mirabilis* (15%), *E. coli*(12%).22% of the amputees each was infected with *Pseudomonas aeruginosa* and *Proteus mirabilis*. Most of the Gram positive cocci were found to be highly resistant to penicillin, gentamicin, and erythromycin. Most gram negative bacilli were highly resistant to antibiotics such as ampicillin, gentamicin, cephalosporins, ciprofloxacin and aztreonam.[19]

In a study carried out by **Murugan S. et al,** they found out that of 2314 (37.82 %) strains of *S. aureus* isolated form diabetic foot ulcers, 992 (42.86 %) were found to be methicillin resistant. More precisely, all MRSA strain (100 %) were resistant to penicillin, 90.92 % to ampicillin, 82.76 % to clotrimoxazole,64.11 % to gentamicin, 60.08 % to erythromycin, 51.91 % to omnatax and 50.10 % to cephalexin. Multi drug resistance for about 7 to 10 antibiotics was observed among 55.0 % of the isolates. However, all the strains were sensitive to vancomycin (100 %).[20]

In a study conducted by **Ahmed T. El-Tahawy** *Staphylococcus aureus* was the commonest isolate being recovered from 28% of cases, including methicillin resistant *staphylococcus aureus* in 9 of 30(30%) patient wounds. The other organisms isolated were *Pseudomonas aeruginosa* (22%) and *Proteus mirabilis*(18%), anaerobic gram-negative organisms (11%) mainly *Bacteroides fragilis*. The antimicrobial susceptibility testing, showed that vancomycin was the most effective against gram-positive and imipenem was the most effective against gram-negative organisms.[21]

**Benjamin A. Lipsky et al. (1997)** conducted a prospective, randomized, multicenter trial compared the efficacy of two antibiotic regimensfor treatment of foot infections in 108 diabetic adults. Patients with infections requiring hospitalization were randomized to receive either intravenous ofloxacin followed by oral ofloxacin or intravenous ampicillin /sulbactam followed by oral amoxicillin/clavulanate (the aminopenicillin regimen) for14-28 days. Patients with osteomyelitis were eligible for the study if the infected bone was to be removed. Of 108 patients enrolled in the study, 88 who were evaluable had various skin and softtissue infections, and 24% had osteomyelitis. For the ofloxacin and aminopenicillin regimens, the mean duration of intravenous therapy was 7.8 and 7.1 days, respectively, the mean duration of oraltherapy was 13.2 and 12.0 days, respectively, the rate of eradication of pathogens was 78% and88%, respectively, and the overall rate of clinical cure or improvement was 85% and 83%, respectively. Thus, about 3 weeks of therapy with either regimen was well tolerated and effective intreating these diabetic foot infections.[22]

According to **Benjamin A. Lipsky et al. (2002)**foot infections in diabetic patients are predominantly caused by gram-positive cocci, many of which are now antibiotic resistant. Because linezolid is active against these pathogens, they compared the efficacy and safety of intravenous and oral formulations with that of intravenous ampicillin-sulbactam and intravenous and oral amoxicillin-clavulanate given for 7–28 days in a randomized, open-label, multicenter study of all types of foot infection in diabetic patients (ratio of linezolid to comparator drug recipients, 2: 1). Among 371 patients, the clinical cure rates associated with linezolid and the comparators were statistically equivalent overall (81% vs. 71%, respectively) but were significantly higher for linezolid-treated patients with infected foot ulcers (81% vs. 68%; $P = .018$) and for patients without osteomyelitis (87% vs. 72%; $P = .003$). Cure rates were comparable for inpatients and outpatients and for both oral and intravenous formulations. Drug-related adverse events were significantly more common in the linezolid group, but they were generally mild and reversible. Linezolid was at least as effective as aminopenicillin/β-lactamase inhibitors for treating foot infections in diabetic patients.[23]

**Benjamin A. Lipsky et al. (2008)** conducted a study on 835 patients who were randomized; those in each treatment arm were similar with regard to demographic and clinical characteristics. Although study 303 failed to demonstrate equivalence, study 304 and the combined data for the 2 trials demonstrated equivalent results (within the 95% confidence interval) for topical pexiganan and oral ofloxacin in clinical improvement rates (85%–90%), overall microbiological eradication rates (42%–47%), and wound healing rates. The incidence of worsening cellulitis (2%–4%) and amputation (2%–3%) did not differ significantly between treatment arms. Bacterial resistance to ofloxacin emerged in some patients who received ofloxacin, but no significant resistance to pexiganan emerged among patients who received pexiganan.[24]

**EktaBansalet al. (2008)** conducted a study on 103patients with diabetic foot lesions to determine their clinical characteristics, the spectrum of aerobic microbial flora and to assess their comparative *in vitro* susceptibility to the commonly used antibiotics. A total of 157 organisms (143 bacteria and 14 fungi) were isolated and an average of 1.52 isolates per case was reported. Polymicrobial infection was found in 35% of the patients. In this study, *Pseudomonas aeruginosa* among the gram-negative (22%) and *Staphylococcus aureus* among the gram-positive (19%) were the predominantly isolated organisms, while *Candida* was the most predominantly isolated fungus. Antimicrobial sensitivity pattern of the isolates is discussed in detail. There was a linear increase in the prevalence of organisms with increase in Wagner's grade. Neuropathy (76%) and peripheral vascular disease (57.28%) was a common feature among the patients. Poor glycemic control was found in 67% of the patients. Awareness about lower limb complications of diabetes was very low (23%) among the patients.[25]

**Dr.Nagesh Malik et al.** conducted a study and total of 75 bacterial isolates were isolated. Ulcers were graded according to Wagner Classification. 53.33% had poly microbial infection whereas mono microbial etiology was observed in 46.67% isolates. Among the total (75) bacterial isolates, gram-positive cocci comprised of 30.66% (23), gram-negative bacilli accounted for 53.33% (40) and pseudomona

species were comprised 16% (12). The ratio for gram-positive: gram-negative: pseudomonas was 1.9: 3.3: 1 respectively.[26]

**Diane M. Citron et al. (2007)** conducted a study that compared ertapenem to piperacillin-tazobactam for the treatment of moderate-to severe diabetic foot infections (DFIs); they obtained 454 pre-treatment specimens from 433 patients. After debridement, the investigators collected wound specimens, mostly by curettage or biopsy, and sent them for aerobic and anaerobic culture. Among the 427 positive cultures, 83.8% were polymicrobial, 48% grew only aerobes, 43.7% had both aerobes and anaerobes, and 1.3% had only anaerobes. Cultures yielded a total of 1,145 aerobic strains and 462 anaerobic strains, with an average of 2.7 organisms per culture (range, 1 to 8) for aerobes and 2.3 organisms per culture (range, 1 to 9) for anaerobes. The predominant aerobic organisms were oxacillin susceptible *Staphylococcus aureus* (14.3%), oxacillin-resistant *Staphylococcus aureus* (4.4%), coagulase negative *Staphylococcus* species (15.3%), *Streptococcus* species (15.5%), *Enterococcus* species (13.5%), *Corynebacterium* species (10.1%), members of the family *Enterobacteriaceae* (12.8%), and *Pseudomonas aeruginosa* (3.5%). The predominant anaerobes were gram-positive cocci (45.2%), *Prevotella* species (13.6%), *Porphyromonas* species (11.3%), and the *Bacteroides fragilis* group (10.2%). Pure cultures were noted for 20% of oxacillin-resistant *Staphylococcus aureus* cultures, 9.2% of *Staphylococcus epidermidis* cultures, and 2.5% of *P. aeruginosa* cultures. Two or more species of *Staphylococcus* were present in 13.1% of the patients. Ertapenem and piperacillin-tazobactam were each active against >98% of the enteric gram-negative rods, methicillin-sensitive *S. aureus*, and anaerobes. Among the fluoroquinolones, 24% of anaerobes, especially the gram-positive cocci, were resistant to moxifloxacin; 27% of the gram-positive aerobes but only 6% of the members of the family *Enterobacteriaceae* were resistant to levofloxacin. Moderate-to-severe DFIs are typically polymicrobial, and almost half include anaerobes.[27]

**Shao Hua Wang et al. (2010)** conducted a retrospective case–control study of 118 (male : female, 68 : 50) Chinese type 2 diabetic patients with foot ulcers (Wagner's grade 3–5) was conducted to determine the prevalence and risk factors for meticillin-resistant Staphylococcus aureus (MRSA) infection in relation to the

original community or hospital parameters. Ulcer specimens were processed for Gram staining,aerobic culture and antimicrobial susceptibility testing. Staphylococcus species were tested for meticillin resistance using oxacillin. *S. aureus* was the most frequent pathogen (25.6 %) in diabetic patient specimens (160 isolates), and a high proportion of *S. aureus* isolates were MRSA (63.4 %). A high percentage of S. aureus isolates (65.4 %) satisfied the definition for hospitalassociated MRSA (HA-MRSA) infection. The size of ulcers [adjusted odds ratio (OR) 1.61; 95 %confidence interval (CI) 1.22–2.12] and osteomyelitis (adjusted OR 18.51, 95 % CI 2.50–137.21) were independent predictors of MRSA infection. The HA-MRSA group had a significantly different distribution from the community-associated MRSA group with respect to age, history of diabetes and length of hospital stay (all P,0.001). Neuropathy, vascular disease (all P50.049) and osteomyelitis (P50.026) were the most common underlying conditions observed in the HAMRSA group.[28]

# AIM AND OBJECTIVES

## SCOPE OF THE STUDY

From the literature review it was found that the prevalence and incidence rate of diabetes increases worldwide especially in India where it is becoming a hub for diabetes. Foot ulceration is a common complication of diabetes that has potentially disastrous consequences for patients.

Better control of blood sugar levels, early recognition of complications of peripheral neuropathy and ischemia, and using a multidisciplinary approach to therapy when an ulcer develops can dramatically reduce this problem.

Primary anti-diabetic therapy includes oral anti-diabetic insulin or combination of both. Supportive therapy includes antibiotics for diabetic foot ulcer and physical measures like routine wound dressing and washing. In antibiotic therapy, much more care should be advised because, over usage of antibiotics produces multiple drug resistance. This produces development of antibiotic resistant strains in the locality.

Prescribing drugs is an essential skill which is required to be continuously assessed and refined accordingly. It not only reflects the physician's knowledge of pharmacology and pathophysiology but also his/her skill in diagnosis and attitude towards selecting the most appropriate treatment. Inappropriate prescription increases the cost of medical treatment and increases morbidity and mortality. The rational use of drugs requires the patients to receive medicines appropriate to their clinical needs. Every health care profession has responsibility to reduce such a crisis like multi drug resistant strains. As a member of health care team, pharmacists have major responsibility to reduce antibiotic resistance.

## AIM

The aim of the present study was to determine the prescription patterns of antibiotics in the management of diabetic foot ulcer.

## OBJECTIVES

- To determine the utilization pattern of antibiotics in the management of diabetic foot ulcer.
- To analyse the therapeutic outcome related to the microbial profile and other demographic and coexisting diseases.

# PLAN OF WORK

The present dissertation work was planned to in order to determine the prescription pattern of antibiotics in the management of diabetic foot ulcer. The present study was conducted in A.J Asirvatham Hospital, in the Department of Diabetology, Madurai.

i. Submission of the protocol for getting the approval from Ethical Committee.
ii. To get the consent letter from the patients.
iii. Select the diabetic foot ulcer patients for the study.
iv. To design the data collection form.
v. Select the monitoring parameters.
vi. Fill the data collection forms with the relevant details.
vii. Collect reports for culture sensitivity from the laboratory.
viii. Determine duration of ulcer.
ix. Check the antibiotics used for each patient.
x. Carry out statistical analysis and recorded.

# METHODOLOGY

**NAME OF THE STUDY**

Prescription pattern of antibiotics in the management in the diabetic foot ulcer in outpatient department.

**STUDY DESIGN**

A perspective cross sectional study was performed on 70 patients to know the prescribing patterns and sensitivity patterns of antibiotics used for the management of diabetic foot ulcer, for six months between February 2013 and July 2013.

**STUDY SITE**

This study was conducted in the diabetic foot clinic in A.J Asirvatham Hospital, Madurai.

**DURATION OF STUDY**

The study was conducted from February 2013 to July 2013.

**STUDY POPULATION**

Patient who visited the diabetic foot clinic in the hospital were included in this study.

**SAMPLE SIZE**

A total of 70 patients were enrolled in the study. The patients who had diabetes and had foot infections were included in this study.

**STUDY CRITERIA**

**Inclusion Criteria**

- Only prescriptions of patients who are diagnosed to have diabetes mellitus with foot ulcer
- Diabetic foot infected patients with either sex.
- Patients aged between 21-90 years.
- Patients diagnosed with both type1 and type 2 diabetes mellitus.
- Patients prescribed with empirical treatment of antibiotics.

**Exclusion Criteria**

- Patients treated with antiviral, antifungal, anti-parasitic as well as selected anti-bacterial, including anti TB agents other than Rifampicin

**PARAMETERS**

A standard data collection form was made and approved by ethical committee. Necessary and relevant data of patients taken by reviewing the patients' data charts containing the history and treatment given. The following were used for data collection.

- Treatment chart
- Patient data collection form(Annexure 1)
- Culture sensitivity report(Annexure 2)

**Analysis of data**

The proposed statistical analysis was done by using mean and standard deviation tests.

**MATERIALS**

1. Patient Proforma (Annexure 1)
   A suitably designed Proforma was used to enter patient data.
2. Culture sensitivity reports (Annexure 2)
   Reports from microbiology laboratory were used.

# RESULTS AND DISCUSSION

## AGE DISTRIBUTION

Ages of 70 cases were studied and were ranged from 21 to 90yrs with the youngest patient being 27yrs and the oldest one 84yrs with the average age being 54.36yrs.

**Table No.1 Distribution of patients according to Age**

| Age | No of Patients | Percentage (%) |
|---|---|---|
| 21-30 | 4 | 5.71 |
| 31-40 | 8 | 11.43 |
| 41-50 | 15 | 21.43 |
| 51-60 | 18 | 25.71 |
| 61-70 | 16 | 22.86 |
| 71-80 | 8 | 11.43 |
| 81-90 | 1 | 1.43 |

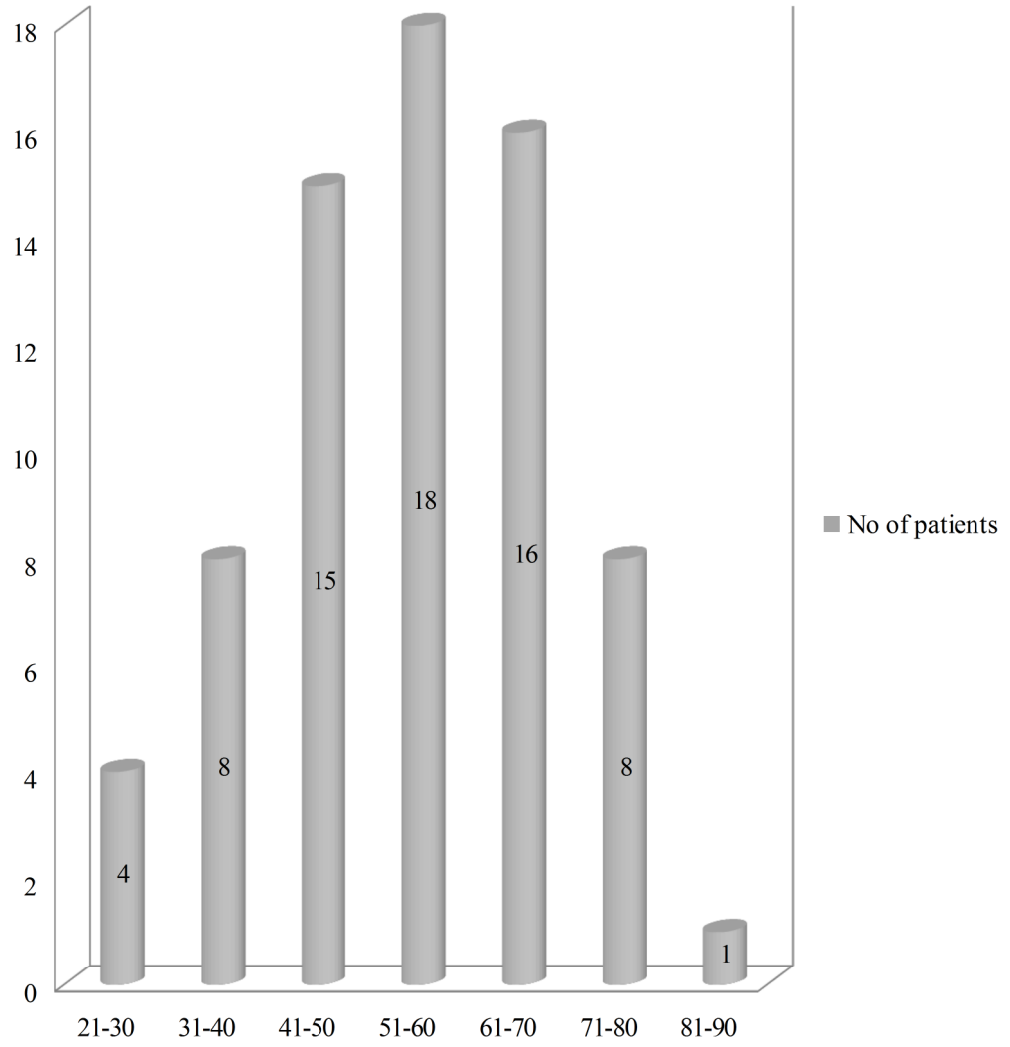



**Fig. No. 1: Age Distribution**

The graph shows that most of the diabetic foot ulcer cases were aged between 51years and 60years.

## GENDER DISTRIBUTION

In the present study out of 70 patients 48 were male patients and 22 were female patients.

**Table No. 2: Gender distribution**

| Gender | Frequency | Percentage |
|---|---|---|
| Male | 48 | 68.57% |
| Female | 22 | 31.43% |
| Total | 70 | 100% |

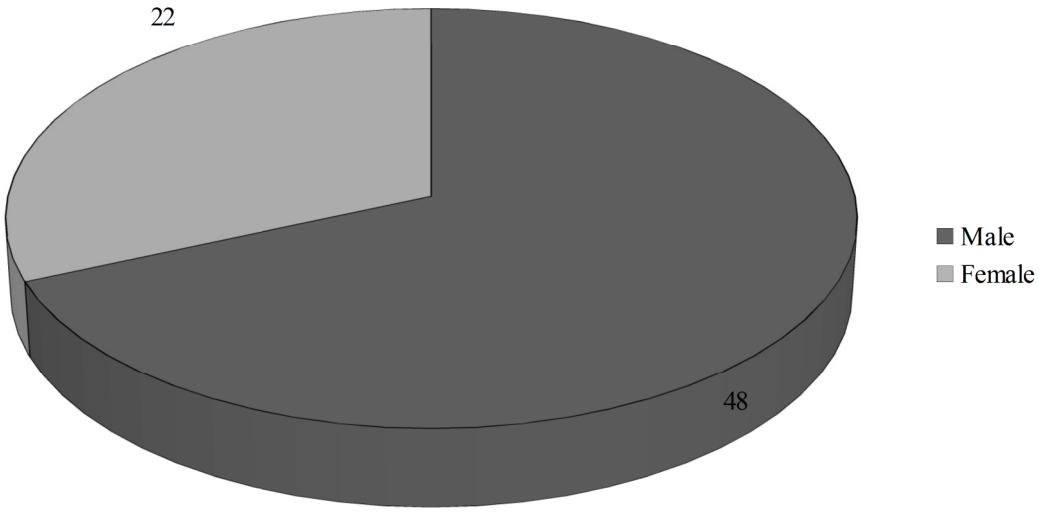



**Fig. No.2: Gender Distribution**

The graph shows male predominance in the occurrence of diabetic foot ulcer.

**PREVALENCE OF DIABETIC FOOT ULCER IN RELATION TO OCCUPATIONAL STATUS OF THE PATIENT**

In this study, the foot ulceration with diabetes was most seen in coolis. This means that patients with no formal education and low level of living status recorded the highest with 35.7%.

**Table No.3 Prevalence of diabetic foot ulcer in relation to occupational status of the patient.**

| Occupational Status | Frequency |
|---|---|
| Cooli | 25 (35.7%) |
| House wife | 17 (24.28%) |
| Govt employee | 8 (11.4%) |
| Farmer | 6 (8.57%) |
| Others | 14 (20%) |

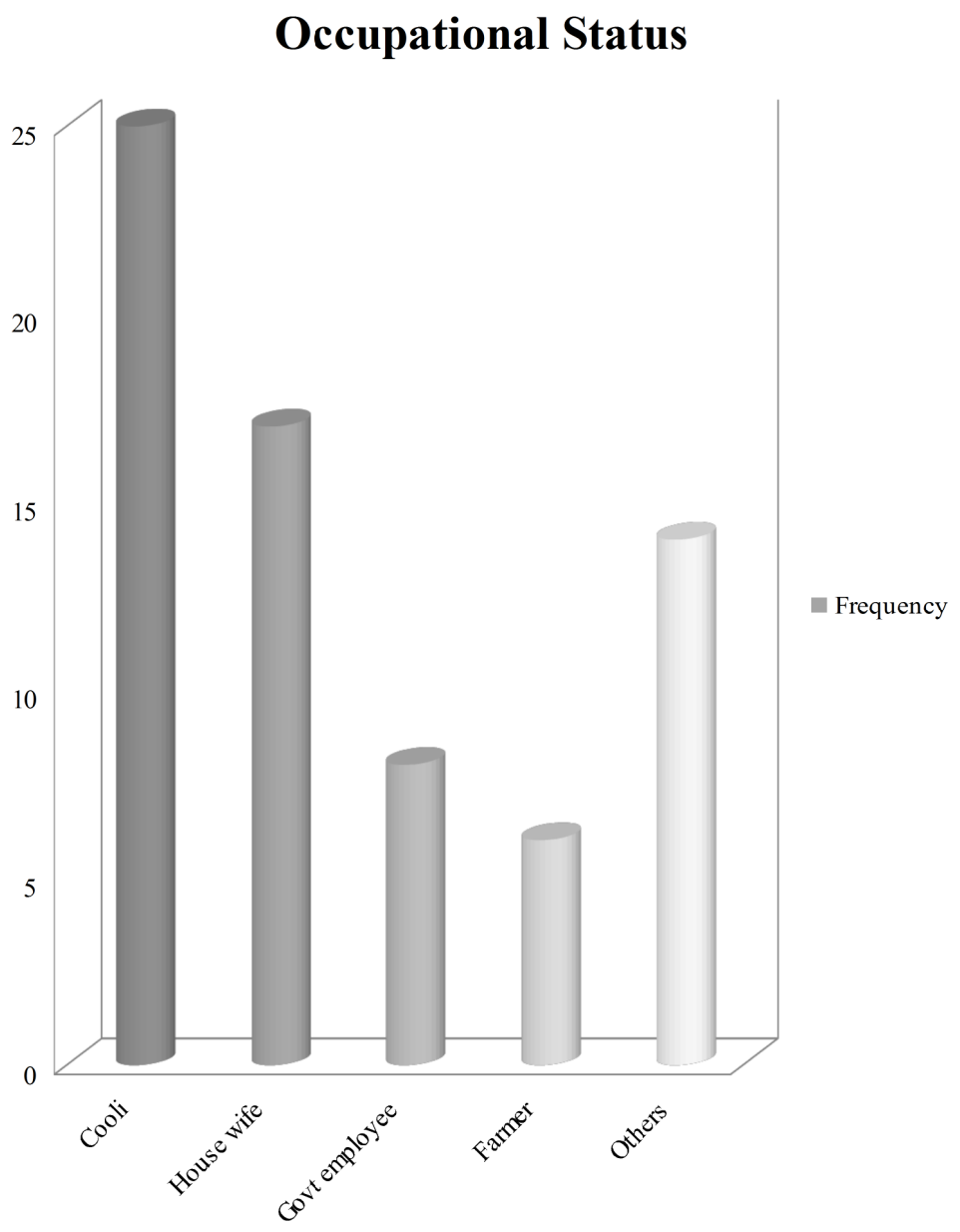



**Fig. No. 2: Occupational status of the patient.**

The graph above shows that people with low living status predominate in the occurrence of diabetic foot ulcer.

**DURATION OF DIABETIC FOOT ULCER**

From this study it is observed that most of the patients presented with foot ulcer of a duration of 3 weeks (27.1%), followed by 2 weeks (22.9%).

**Table No.4 showing duration of Diabetic Foot Ulcer**

| Duration | No. of Patients | Percentage |
|---|---|---|
| 1 week | 5 | 7.1% |
| 2 weeks | 16 | 22.9% |
| 3weeks | 19 | 27.11% |
| 1 month | 13 | 18.6% |
| 2 months | 5 | 7.1% |
| 3months | 1 | 1.4% |
| 4 months | 1 | 1.4% |
| 5 months | 1 | 1.4% |
| 6 months | 4 | 5.7% |
| 7 months | 2 | 2.9% |
| 8months | 1 | 1.4%5 |
| 9months | 1 | 1.4% |
| Above 10 months | 1 | 1.4% |

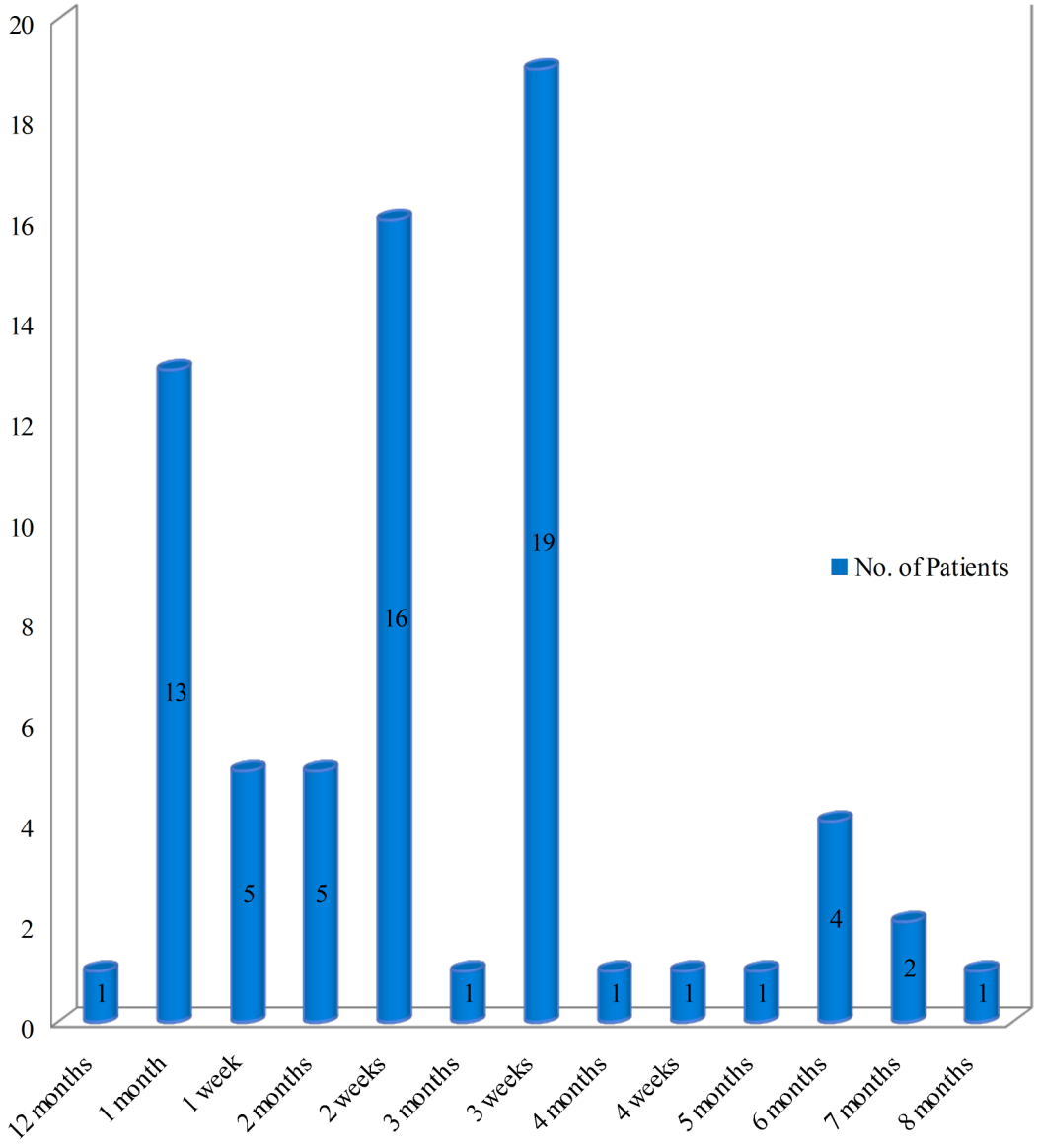



**Fig.No.4 Duration of diabetic foot ulcer**

## PATIENT'S DIABETIC HISTORY

**Table No.5 Patient's diabetic history during the study**

| | |
|---|---|
| Type 2 DM | 68 (97.1%) |
| Type 1 DM | 2 (2.9%) |
| Duration of DM (Mean+SD) | 2-36yrs (12.80 ± 6.85) |
| FBS Mean + SD | 147.67 ±12.86) |
| PPBS Mean + SD | 210.1 ±21.86 |
| Known Family History of DM | 52 (74.29%) |
| Controlled DM cases | 25 (35.7%) |

## COMORBIDITIES

**Table No.6 Patient's comorbidities with DM**

| Comorbidities | Frequency | Percentage |
|---|---|---|
| Hypertension | 20 | 28.6 |
| Peripheral vascular disease (PVD) | 2 | 2.9 |
| Cardiac diseases | 1 | 1.4 |
| Hypertension + Peripheral vascular disease | 9 | 12.9 |
| Hypertension + Cardiac diseases | 3 | 4.3 |
| Hypertension + Renal problems | 1 | 1.4 |
| Hypertension + PVD + Cardiac diseases | 12 | 17.1 |
| Cardiac diseases + Renal problems | 1 | 1.4 |
| Hypertension + PVD + Renal problems | 1 | 1.4 |
| Hypertension + Cardiac + Renal problems | 2 | 2.9 |
| Hypertension + PVD + Cardiac + Renal | 5 | 7.1 |
| Hypertension + PVD + Cardiac + Others | 1 | 1.4 |
| Nil | 11 | 15.7 |
| Others | 1 | 1.4 |

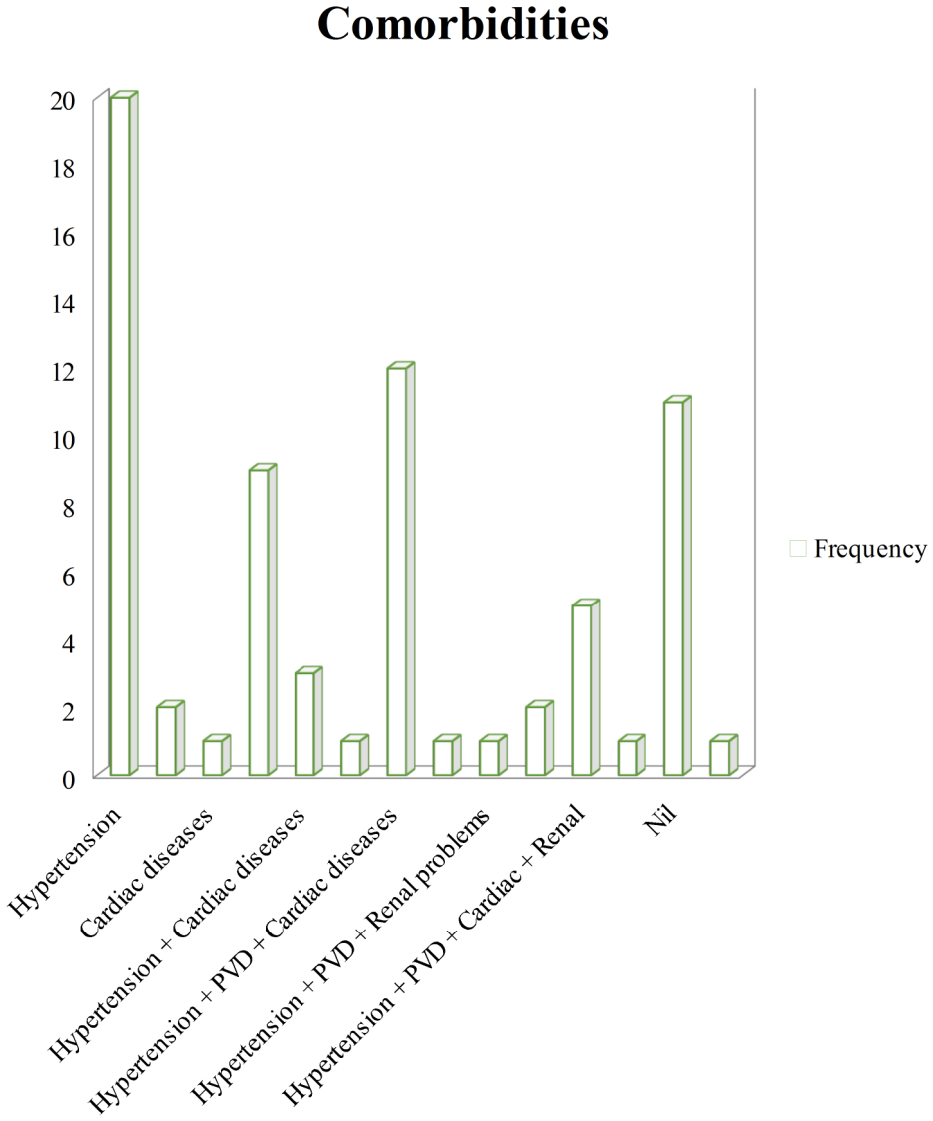
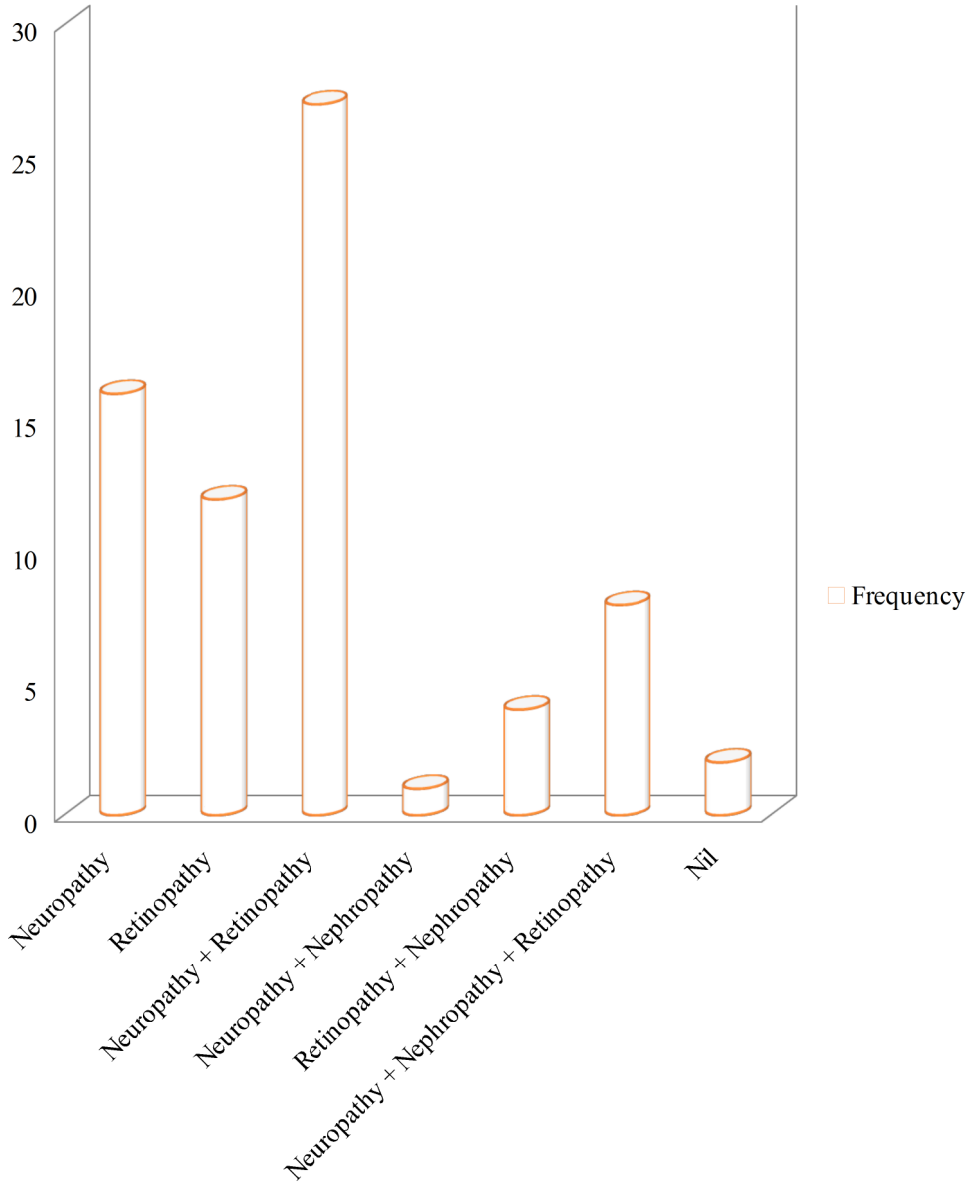



**Fig. No.5 Patient's Comorbidities with DM**

## COMPLICATIONS OF DIABETES MELLITUS

**Table No.7 Patient's diabetes complications**

| Complications | Frequency | Percent |
|---|---|---|
| Neuropathy | 16 | 22.9 |
| Retinopathy | 12 | 17.1 |
| Neuropathy + Retinopathy | 27 | 38.6 |
| Neuropathy + Nephropathy | 1 | 1.4 |
| Retinopathy + Nephropathy | 4 | 5.7 |
| Neuropathy + Nephropathy + Retinopathy | 8 | 11.4 |
| Nil | 2 | 2.9 |




**Graph No. 6: Complications of Diabetes Mellitus**

It was observed that neuropathy was the most common complication of diabetes mellitus with 16 cases out of 70 patients. 27 patients suffered from both neuropathy and retinopathy.

## TYPE OF WOUND

**Table No.8 Type of diabetic wound**

| Stages | No of Patients | Percentage |
|---|---|---|
| Stage A | 7 | 10% |
| Stage B | 28 | 40% |
| Stage C | 5 | 7.14% |
| Stage D | 30 | 42.86% |

From this table stage D shows highest no of patient suffering from Diabetic foot ulcer.

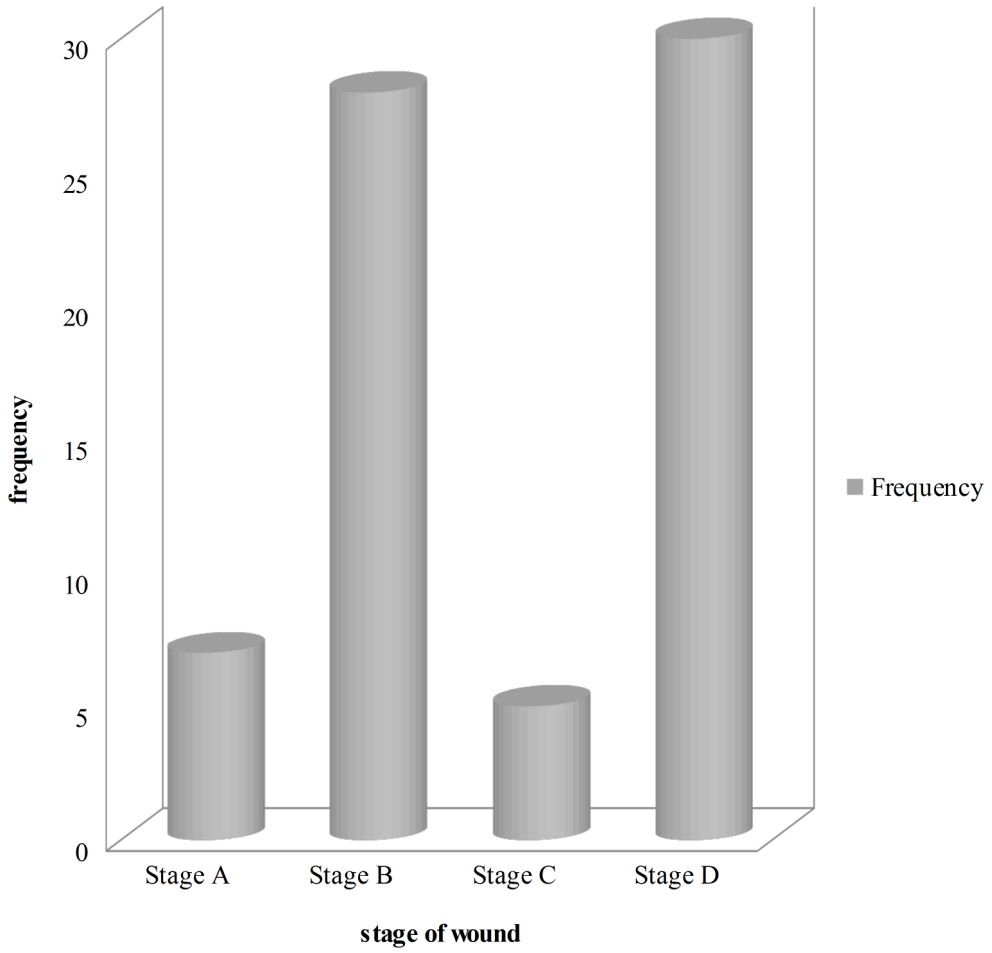



**Fig. No. 7: Type of Wound**

Of the 70 patients, 30 of them showed signs of both infection and ischemia (stage D). 58 patients showed signs of infection.

**FREQUENCY DISTRIBUTION OF ORGANISMS ISOLATED FROM DIABETIC FOOT CASES.**

**Table No.9 Organisms isolated from 70 diabetic foot cases.**

| Causative Organism | No. of cases | Percentage |
|---|---|---|
| Staphylococcus aureus | 28 | 40% |
| Pseudomonas | 11 | 15.7% |
| Klebsiella | 9 | 12.8% |
| Streptococcus spp | 12 | 17.1% |
| MRSA | 2 | 4.3% |
| Escherichia coli | 1 | 1.4% |
| Proteus vulgaris | 3 | 4.2% |
| Staphylococcus + E. Coli | 1 | 1.4% |
| Klebsiella + P. Vulgaris | 1 | 1.4% |
| Sterile | 2 | 2.9% |
| Total | 70 | 100% |

From this table *Staphylococcus aureus* organisms accounts for the highest no of cases.

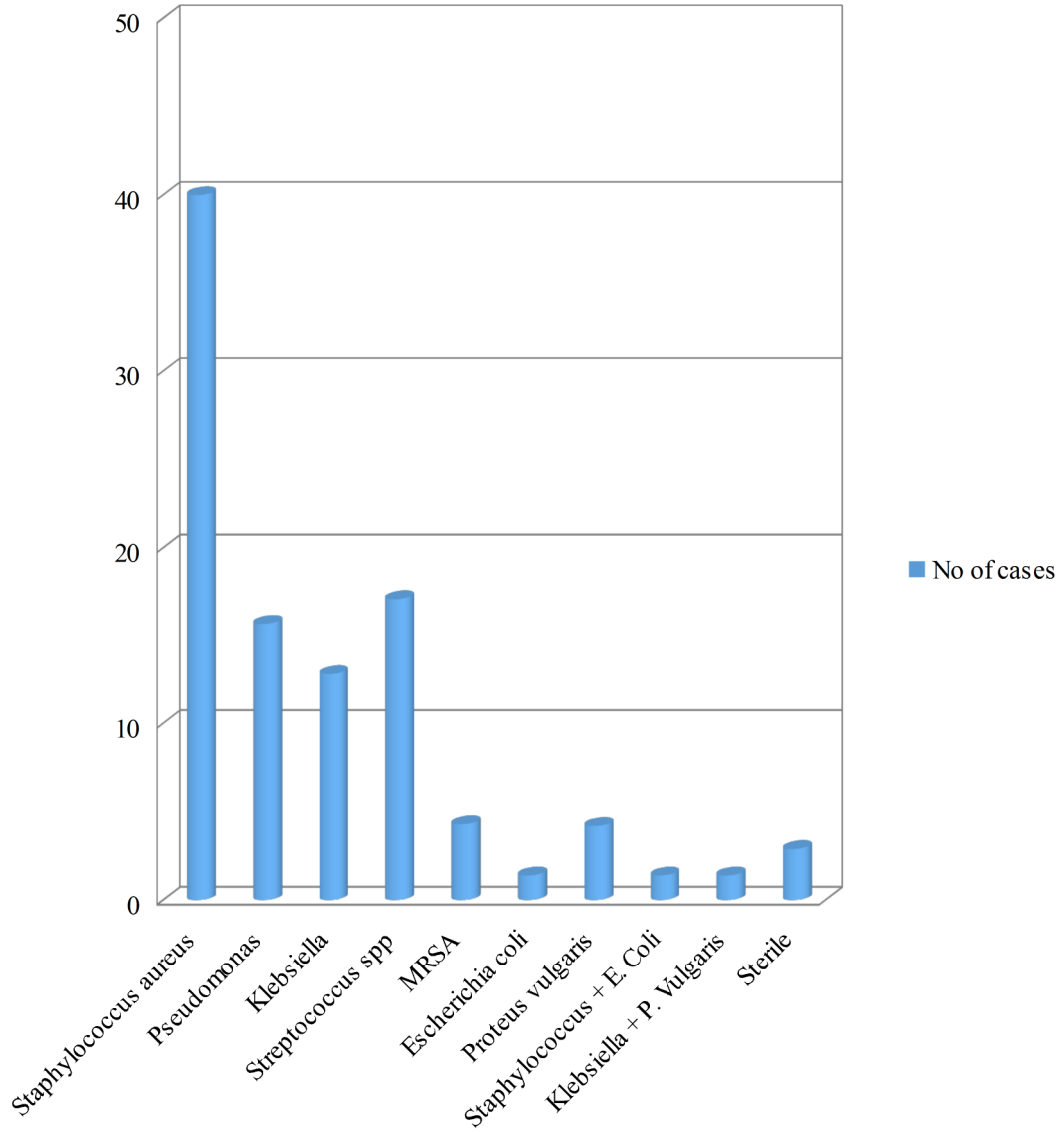



**Fig No 8: Organisms isolated from the diabetic foot ulcer.**

## DISTRIBUTION OF GRAM NEGATIVE BACTERIA

**Table No. 10: Distribution of Gram Negative bacteria**

| Gram Negative organism | No. of organisms |
|---|---|
| Pseudomonas | 11 (45.8%) |
| Escherichia coli | 1 (4.2%) |
| Klebsiella | 9 (37.5%) |
| Proteus Vulgaris | 3 (12.5%) |

Pseudomonas is responsible for most No of Gram Negative infections.

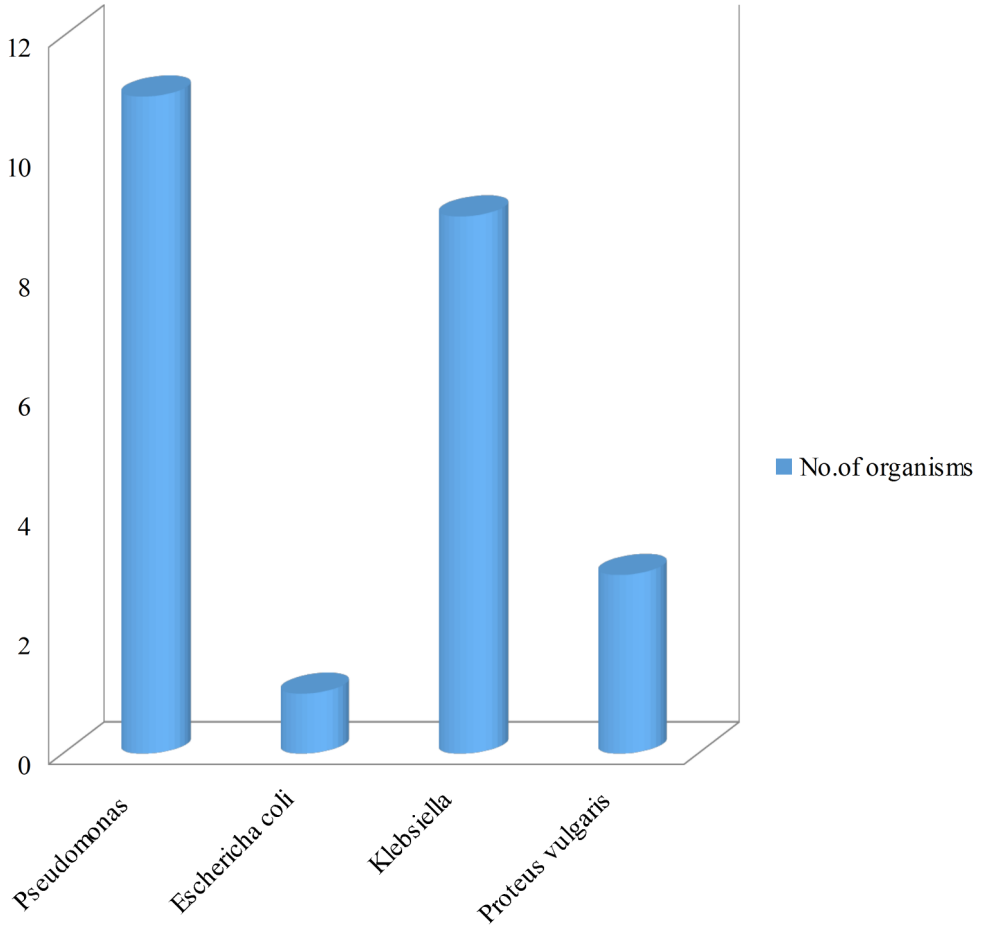



**Fig No.8:Distibution of Gram Negative Bacteria.**

## DISTRIBUTION OF GRAM POSITIVE BACTERIA

**Table No.11: Distribution of Gram Positive bacteria**

| Gram Positive Organism | No. of Organisms |
|---|---|
| Staphylococcus aureus | 28 (59.5%) |
| Streptococcus spp | 12 (28.6%) |
| MRSA spp | 2 (8.3%) |

Staphylococcus aureus is responsible for the most no of Gram Positive infection.

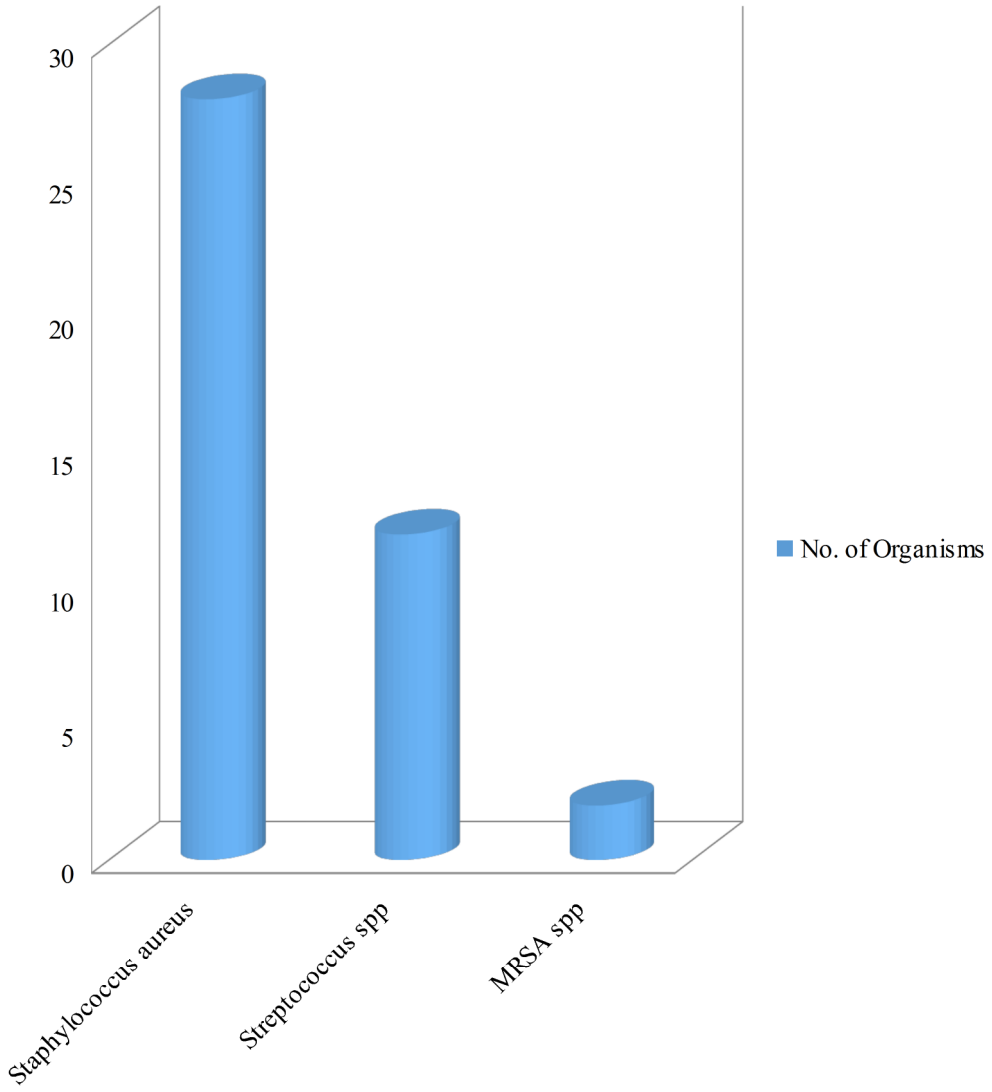



**Fig No.10: Distribution of Gram Positive Bacteria**

## PRESCRIBING PRACTICE OF ANTIBIOTICS IN DIABETIC FOOT ULCER

**Table No.12: Antibiotics used in diabetic foot clinic.**

| Antibiotic | Frequency | Percentage (%) |
|---|---|---|
| Linezolid | 2 | 2.5% |
| Levofloxacin | 26 | 32.1% |
| Cefuroxime | 28 | 34.6% |
| Amikacin | 15 | 18.5% |
| Cefotaxime | 2 | 2.5% |
| Amoxicillin + Clavulanic acid | 7 | 8.6% |
| Vancomycin | 1 | 1.2% |

From this table cefuroxime was the most prescribed antibacterial for diabetic foot ulcer.

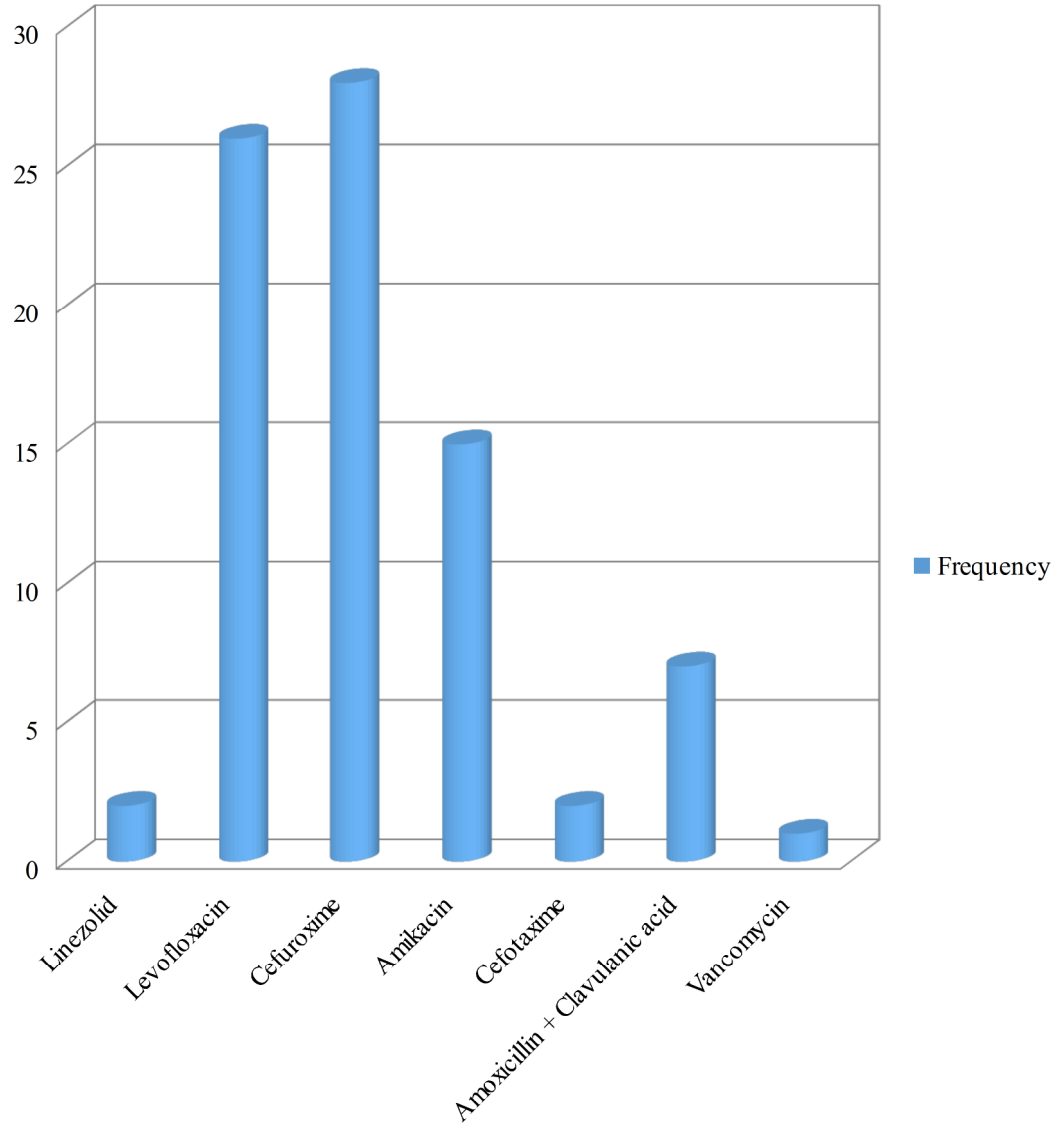



**Fig No.11: Antibiotics used in diabetic foot clinic.**

# DISCUSSION

A total of 70 patients who fulfilled the inclusion criteria and who were to the diabetic foot clinic in A.J Asirvatham Hospital, Madurai, were included in this study. The study was carried out for a period of six months from February 2013 to July 2013.

Among the 70 patients with diabetic foot infections from 68.57% were male and 31.43% were female. The study group consisted of population between 21 to 90yrs with youngest patient of 27yrs and oldest 84yrs with average being 55.5yrs.The mean age of the study population was 54.36years. In thisstudy,most of the male patients were labours and farmers who were prone to injury leading to infection, whereas most of the female patients were house wives. This may be an important factor for male preponderance. In this study most of the patients were coolies and farmers, who had low living status, thus the male patients suffered more than the female patients because of diabetic foot ulcer.

The type 2 diabetes was more common than type 1 diabetes. In the study 97.1% patients had type 2diabetes and only 2.9% had type 1 diabetes. It is observed that the incidence of type 2 diabetes increases with age and with increasing obesity.It is observed that the patients' mean Fasting Blood Sugar (FBS) and Post-Prandial Blood sugar (PPBS) values of the patients were also high, 147.67±12.86 and 210.1±21.86 and the distribution of uncontrolled case were very high.

In this study it is shown most of the patients had known family history 71.8%. This showed that, the occurrence of diabetes mellitus was closely related to genetic pre-disposing factors. Also in this study, the minimum duration of diabetes mellitus was 2yrs and maximum 34yrs with mean duration 12.89 years.This indicates that incidence of risk of diabetic foot ulcer increases with diabetes with long duration. In most cases the duration of diabetic foot range was between 2weeks to 3weeks with the highest being 3 weeks(27.1%). So, the present study assumes that in a short duration of time the foot ulcer becomes a burden for most of the patients. It is therefore significant in the Indian context where the disease is detected in later stages.There is also little awareness for foot care in patients and a significant delay in seeking the treatment. Further a significant population in rural area work in the fields with barefoot thus increasing the chance of further infection.

It observed that the common comorbid illness seen in this population were hypertension (28.6%), PVD (2.9%) and cardiac diseases (1.4) with the three comorbid illness making up a total of 12 (17.1) of the cases. Therefore hypertension patientsandperipheral vascular diseases patients ought to take possible care towards diabetic foot ulcer.

In the diabetic foot clinic neuropathic foot cases were common. The most common complicationsof diabetes in population were identified as neuropathy (22.9%) retinopathy (17.1%) and nephropathy and neuropathy (1.4%) making the least number of cases.

The study illustrated the prevalence of wounds based on the University of Texas Wound Classification System (UTWCS). In all wounds 42.86% had signs both infection and ischemia (stage D), and a further 40% had signs of infection (stage B).In total 58 wounds (stages B&D) showed signs of infection. It meant that the population had epithelialized wounds, superficial wounds and osteomyelitis may also be present.

The study illustrated that infection is due to Gram-Positive Cocci, Gram-Negative Bacilli and polymicrobials.

It was observed that out of 70 cultures, two cases weresterile,and thus did not contain any growth. Of the remaining 68 bacterial cultures, 35.29% were gram-negative bacilli whereas 64.71% were Gram-Positive Cocci. Out of which three types of Gram-Positive Cocci and four types of Gram-Negative Bacilli were recorded. Our study revealed that *Klebsiella* (37.5%), *E. coli* (4.2%), *Pseudomonas* (45.8%) and *Proteus vulgaris* (12.5%) were the most common Gram-Negative organisms isolated. *Staphylococcus aureus* (59.5%), *Streptococcus* (28.6%) and MRSA (8.3%) were the most common Gram-Positive pathogen isolated in the study.

In the diabetic foot clinic, *Staph.aureus*was isolated as most common pathogen, (40%), followed by *Streptococcus spp.* (17.1%).

According to David B.S, extended-spectrum β-lactamaser (ESBL) producing organisms are an increasing problem for practitioners dealing with infectious disease.

*Escherichia coli, Klebsiella pneumonia* and *Klebsiellaoxytoca* are the most common ESBL-producing pathogens[34].

In this study of70 cases inthe diabetic feet clinic and only stage B and stage D wounds were treated with antibiotics.

In this study the commonly used antibiotics were different.

Out of 70 patients in the diabetic foot clinic the most prescribed antibiotic was Cefuroxime (34.6%) followed by levofloxacin (32.1%), amikacin (18.5%), amoxycillin+clavulanic acid (8.6%). The other antibiotics used in diabetic foot clinic include; Linezolid (2.5%), cefotaxime(2.5%) and vancomycin(1.2%) .

It was observed that levofloxacin and cefuroxime were the most frequently prescribing antibiotics.

# SUMMARY

This study was carried out because diabetic foot infections are such an important cause of hospitalization which may result in foot amputation and disability and secondly, there is no generally accepted standard guideline for antibiotics used for diabetic foot ulcers.

A total of 70 patients who fulfilled the inclusion criteria, were enrolled in this study for a period of 6 months between February 2013 and July 2013.The culture and sensitivity reports of 70 patients prescribed with antibiotics empirically were studied.

The study revealed that patients had diabetic foot ulcer which may include cellulites and gangrene. This study also showed that, necrotic wound and ischemic cases were present in the diabetic foot clinic.

We found that, the antibiotics used for treating foot ulcer, in the study groups included cefuroxime was the most commonly prescribed empirical drug in diabetic foot clinic, followed by levofloxacin, cefotaxime,,amikacin, amoxicillin and clavulanic acid, linezolid and vancomycin alone or in combination were used.

It noticed that these above drugs were empirically used antibiotics for diabetic foot ulcer in the hospital.

In microbiological sensitivity testing, three types of Gram-Positive Cocci and four types of Gram–Negative bacilli were isolated. The culture reports, revealed that Gram–Negative pathogens were more resistant to cephalosporins whereas grams – positive pathogens were more sensitive to cephalosporins. *Staphylococcus aureus*was found in 28 (40%) cases therefore, predominated, followed by*Streptococcus*12 (17.1%5) then*Pseudomonas*11 (15.7%).

It is important to take care such that, before starting any antibiotic regimen, the wound tissue or swab should be collected as much as possible and find out the sensitivity pattern. This will identify the microorganisms which are present. This in turn helps to reduce the multi-drug resistance crisis. Treatment failure could probably be due to nosocomial infection and antibiotic resistance developed by the organisms.

# CONCLUSION

Diabetic foot infection by Gram-Negative pathogens was found to be more resistant to the commonly prescribed antibiotics whereas, Gram-Positive have shown increased sensitivity to cephalosporins and also the presence of nosocomial gram-positive and gram-negative pathogens is a matter of concern.

The bacteriology showed a high rate of multiple resistances to commonly used antibiotics. This is mainly due to ready availability and the easy access to those antibiotics by the general population, without medical prescription. Proper measures should be taken to resolve this solution.

Hence there should be an active infection control team, which can monitor the prevalent organisms and their antibiograms, and periodically inform the clinicians. The pharmacist should also be included in the team apart from other medical and paramedical staff.

The sensitive part of organisms to antibiotics may be different in different places, in the same community. Regular monitoring of culture and sensitivity reports is needed for selecting drugs for the empiric therapy.

Implementation of antibiotic policy in the hospitals helps to properly audit of antibiotic usage as well as purchase procedures.

Clinical pharmacists facilitate anti-microbial restriction program may have to be introduced to limit the antimicrobial resistance. Hence in conclusion the culture sensitivity testing is an important factor before determining antimicrobial therapy.

When the pus sample is sent for culture and sensitivity testing, is should be informed to the microbiologist to test for the empirical drug, which is being used on the patient.

This study concludes that even, empirically used antimicrobials also had low sensitivity pattern. There for while going for the treatment of antibiotics therapy on empiric basis, till the laboratory culture sensitivity reports.

In microbiology lab, it is not possible to be done the sensitivity analysis for all the antibiotics, which are performed only for few numbers. The basis for selection in the analysis of antibiotics not known. So the culture sensitivity reports will not be conclusive for sensitivity pattern.

Treating physicians should design a requisition form depicting the organisms isolated and their antibiograms during first culture and repeat culture, so that it becomes easy for him to decide what drugs can be used in patients.

Since the facilities in the hospitals setting are limited a strict aseptic condition could not maintain. This may contribute to some sort of contamination during sample taking. This may adversely affect the culture and sensitivity results.

Multidisciplinary approach is required for efficient management of these patients with diabetic foot infections.

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# ANNEXURE

## PROFORMA

| | | | |
|---|---|---|---|
| Name: | Age: | Sex: | IP: |
| Address: | Occupation: | DOA: | DOD: |

Duration of ulcer: Duration of ulcer:

Co-morbid illness: Hypertension, PVD, Cardiac disease, Renal disease, others.

Medical history:

Complications of diabetes:

General examination:

Systemic examination:

Examination of ulcer: UTWCS:

Investigations:

FBS :

PPBS :

Culture :

Any other relevant information:

Follow up:

| DRUG | DOSE | ROUTE | FREQUENCY |
|---|---|---|---|
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